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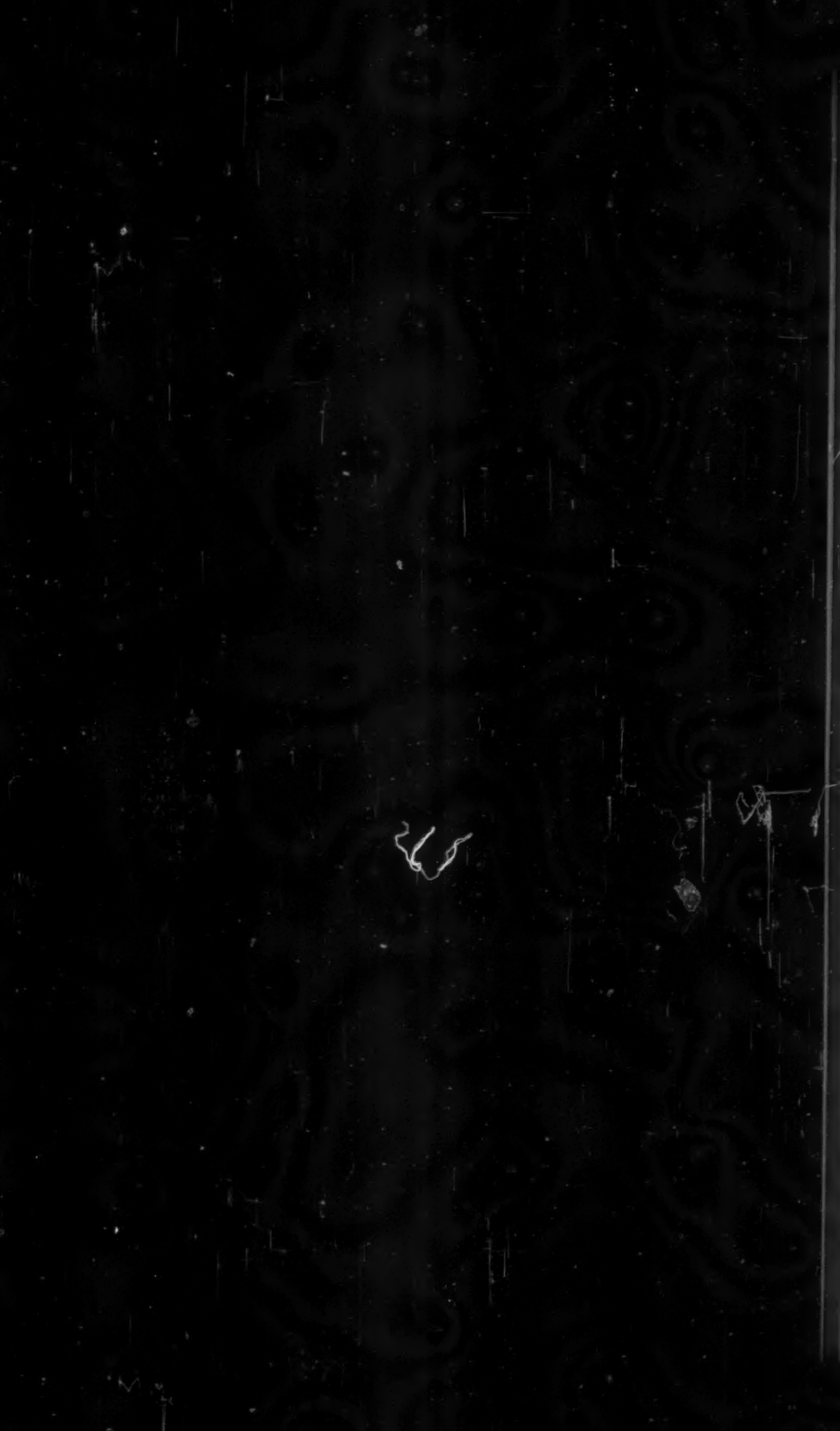

# CONGENITAL ANEURYSMAL DILATATION OF THE AORTA ASSOCIATED WITH ARACHNODACTYLY

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Received for publication March 30, 1943

Congenital malformations of the heart are known to be of frequent occurrence in persons with arachnodactyly. Ellis (1) estimated that of the patients with this skeletal abnormality one-third had a malformation of the heart. In a previous report one of us (2) discussed the frequency with which interauricular septal defects are found in association with this anomaly. Piper and Irvine-Jones (3) also have emphasized this fact. In the following two cases there was a malformation of an entirely different nature:—there was an extraordinary aneurysmal dilatation of the ascending portion of the aorta proximal to the aortic arch. Histological examination of the aorta showed that the dilatation was caused by a congenital abnormality of the media. Therefore, the two cases are reported in detail.

## CASE I

F. D., a white girl, born in 1924. She was under the care of one of us (R. W. B.) throughout her life.

*Family history* negative except that a paternal uncle has a congenital malformation of the heart.

*Past History.* At birth the eyes were noted to be unusually prominent and the fingers and toes abnormally long. Scoliosis developed shortly after the patient began to walk and became progressively worse throughout her life. Difficulty in vision was not noticed until the child started to school. During childhood she suffered from vague pains in her legs and had occasional epistaxes but never had a definite attack of acute rheumatic fever.

*Physical Examination* (November 1937—13 years old) revealed a tall thin girl with marked thoracic and lumbar scoliosis and shortening of the chest. The eyes were unduly prominent, and there was anterior dislocation of both lenses. The extremities were extremely long and slender (see Plate 1). There was marked hyperextensibility of the fingers. Both ankles showed a marked inversion; both feet were flat; and the first and second toes on both feet were of the hammer type.

[1] Frederick, Maryland.

The heart was enlarged and lay transversely in the chest, causing a deformity of the left chest. The apex beat was palpable outside the mid-clavicular line. There was a pronounced systolic thrill and a loud systolic murmur, both of maximal intensity over the sternum. The murmur was well heard to the right of the sternum and was transmitted to the vessels of the neck. The murmur was so loud that it could be heard by the unaided ear at a distance of two inches from the chest. In addition there was a faint early diastolic murmur audible over the base of the heart and along the left sternal border. The blood pressure in the arm was 148 systolic, 90 diastolic. The blood pressure in the leg was not recorded, but there was a strong pulse in the dorsalis pedis. The lungs were clear. The abdomen was essentially negative. The liver, spleen, and kidneys were normal in size and position. The genitalia were normal. The extremities were as previously described.

The chest deformity and the displacement of the heart rendered it difficult to evaluate the roentgenographic and fluoroscopic findings (see Plate 2). The heart was also seen to be enlarged in both oblique views. Upon the administration of barium the esophagus could be seen to be displaced backward by the left auricle. The electrocardiogram showed a P-R interval of 0.20–0.22 of a second and notching of $R_1$ and $R_2$ and $S_3$ but did not show any axis deviation.

*Clinical Diagnosis.* Arachnodactyly, congenital dislocation of the lenses, and congenital malformation of the heart. The possibility of an interauricular septal defect with a superimposed rheumatic infection was considered because of the frequency with which this type of septal defect has been reported in association with arachnodactyly. Against this diagnosis was the enlargement of the left auricle. The enlargement was thought to be explicable on the basis of the chest deformity and therefore to be apparent rather than real.

During the following year the patient developed auricular fibrillation. On November 2, 1938, she dropped dead.

Autopsy, *J.H.H. No. 16613A*, was limited to the heart and aorta, which were removed from the body after it was embalmed. On gross examination the heart was markedly enlarged; it weighed 560 grams after fixation. There was only a moderate amount of epicardial fat. The epicardium was smooth. The enlargement of the heart was primarily due to the great hypertrophy of the left ventricle. The endocardium of the right auricle was smooth. The foramen ovale was quite large, measuring 4.5 cm. in diameter. The greater part of it was covered by a valve, but at its upper margin there was a slit-like aperture opening into the left auricle which measured 1.5 cm. in length. The margins of the aperture were thickened and the valve itself was wrinkled. The tricuspid and pulmonary valves were normal and delicate. Their orifices measured 14 cm. and 8 cm. respectively. The right ventricle was normal. Its wall measured 4 mm. in thickness. The left auricle was dilated and slightly hypertrophied. The opening at the upper margin of the foramen ovale offered free communication between the two auricles, but the valve covering the greater part of the foramen was closed in the normal fashion from left to right. In the endocardium of the left auricle, between the mitral valve and the foramen ovale there was a wrinkled, roughened patch such as is so frequently seen in an old rheumatic infection. The mitral leaflets were thickened

and rolled; the mitral orifice measured 14 cm. in circumference. The left ventricle was greatly hypertrophied and only slightly dilated; the wall measured 22 mm. in thickness. The endocardium was smooth. The aortic leaflets were normal. The aortic ring was wide, measuring 9 cm. in circumference. Immediately above the ring the ascending aorta was greatly dilated, forming an aneurysmal sac which was fusiform in shape (see Plate 3) and attaining a maximum circumference of 14 cm. Just proximal to the origin of the innominate artery this aneurysmal dilatation came to an abrupt end, and the aorta narrowed to a circumference of 5 cm. Except for slight wrinkling in the region of the right coronary orifice, the endothelium was smooth. In the arch of the aorta and also in the thoracic aorta there were a few small streaks of intimal fat. The aorta, even in the dilated portion, was of normal elasticity. The orifices of the coronary arteries were located abnormally high above the aortic valves. The arteries were, however, entirely normal. No remnant of the ductus arteriosus could be found.

*On microscopic examination* the myocardium of the left ventricle showed hypertrophy, but there was no scarring suggestive of an old rheumatic infection. The section of the endocardium taken from the roughened patch from the left auricle showed some thickening, but no other lesion. The mitral valve was slightly thickened by connective tissue but the endocardium was smooth. The coronary arteries were normal.

The aorta, in the region of the fusiform dilatation, showed a remarkable change in the structure of the media. The entire media was involved, both the muscular layer and the elastic tissue. The changes were most pronounced in the sections taken from the dilated portion of the aorta, but were also present throughout the entire length obtained at autopsy, which included the thoracic portion of the descending aorta. Thus microscopic examination revealed changes even in the portion of the aorta which on gross examination appeared to be entirely normal. The lesion consisted of a rarefication of the media and a total disarrangement of the elastic tissue. There were no distinct internal or external elastic lamellae. The medial elastica was rarefied and fragmented in some places and in many places it was lacking. The abnormality also involved the musculature of the media. The muscle bundles were distinctly atrophic. Furthermore, instead of lying parallel to one another in the normal fashion, the muscle fibers branched in all directions in a totally irregular fashion. These irregular branching muscle bundles were separated by cystic spaces containing coagulum which stained blue with hematoxylin and eosin. In some places these spaces were small and appeared as clefts (or elongated openings) distributed between the muscle fibers and running parallel to them; in many places they became confluent and formed large irregular cystic-like spaces. In the region of the aneurysm the structure of the media was further distorted by the presence of numerous large, irregular blood channels which arose from the adventitia and penetrated the media. Except for the abnormal blood channels the adventitia was normal. The intima showed only slight connective tissue thickening. In none of the sections was there any evidence of fresh necrosis, degeneration, or cellular infiltration (see Plate 4).

*Anatomical Diagnosis.* Arachnodactyly; aneurysmal dilatation of the aorta due to congenital malformation of the media; cardiac hypertrophy, especially of left ventricle; incomplete closure of foramen ovale; scarring of mitral valve.

CASE II

*R. C.* (J.H.H. No. 155970).[2] A colored male, born in 1913, was admitted to the Medical Service December 1938, complaining of precordial pain.

*Family History.* The paternal grandfather and father both were said to have been tall and slender and to have had long, thin arms. The father had poor eyesight. The patient's maternal grandmother and mother were of normal habitus; the latter was examined and showed none of the stigmata of arachnodactyly. The patient's mother and father were third cousins. A full brother of the patient was said to have been of normal habitus.

*Past History.* The patient was of slender build. At the age of six years the chest was noted to be misshapen. At the age of nine the patient began to complain of poor vision. In 1927 at fourteen years of age on examination in the eye clinic the vision in both eyes was found to be 20/200. The patient grew in stature very rapidly and at the age of fifteen had attained full height. In 1929 he was admitted to the Orthopedic Service for surgical correction of a marked eversion of the left ankle. At that time the examination of the heart revealed a rough presystolic murmur. Ether anesthesia was administered without incident. During succeeding years the man worked as a laborer without any complaints relative to his heart. There was no history of rheumatic fever.

*Present Illness.* In February 1938 at the age of 25 years, the patient had his first attack of precordial pain, it followed exertion and was relieved by rest. The pain radiated into the left shoulder and down the left arm. Examination in the Medical Out-Patient Clinic in June 1938 revealed findings similar to those noted on admission to the Medical Service in December 1938 as recorded below. The complaint at the time of admission to the hospital was the increasing frequency of the attacks of pain.

*Physical Examination* on admission to the J.H.H. Medical Service (December 1938) revealed the patient to be an asthenic, twenty-five year old negro, 73 inches in height and weighing 144 pounds. His posture was poor due to a two-inch shortening of the left leg with consequent thoracic and lumbar scoliosis. The inner ends of both clavicles were slightly dislocated upward. The fingers were moderately long and tapering and were slightly webbed. They did not show any clubbing or cyanosis. The left foot was flat. There was bilateral hallux valgus, and there were several hammer toes. There was a defect in the arch of the sacrum demonstrable by palpation and roentgenogram. The frontal area of the head was

[2] The authors are indebted to Dr. Palmer Futcher and the Medical Department of the hospital for the opportunity to include this case.

prominent and the palatal arch high. Both optic lenses were found to be dislocated upward and outward. Vision was 3/200 in one eye and 20/50 in the other.

The heart was markedly enlarged especially in the region of the left ventricle, and the pulmonary conus appeared moderately enlarged (see Plate 5). Neither the aorta nor the left auricle impinged upon the barium-filled esophagus. A precordial thrill was noted, but the timing varied from observer to observer. On auscultation the rate and rhythm were normal. A presystolic rumble was heard at the apex. At the base, loudest in the second and third interspaces to the left of the sternum, there was a loud, coarse, systolic murmur and a loud, blowing, diastolic murmur. The blood pressure in both arms was 125 systolic, 50 diastolic; the pulse was not definitely collapsing.

The abdomen was negative. The liver, spleen and kidneys were not palpable. The genitalia were normal. The extremities were as previously described.

The electrocardiogram showed a P-R interval of 0.21 of a second; T waves were normal except when the patient was receiving digitalis.

Rebreathing caused an attack of angina pectoris.

Serum albumin, globulin, calcium, phosphorus, cholesterol, phosphatase, nonprotein nitrogen, and sugar were normal. Serological tests for syphilis were negative. Basal metabolic rate was normal. The sella turcica was small and shallow. The cortex of the long bones was somewhat thin.

The patient was discharged after two weeks. For a while his attacks of exertional angina were successfully controlled by nitroglycerine. The control of the pain became progressively more difficult. Two subsequent admissions were necessitated by intractable precordial pain. In October 1939 during his fourth admission the patient died suddenly.

*Clinical Diagnosis.* Arachnodactyly, congenital dislocation of the lenses, and congenital malformation of the heart. There was no agreement as to the nature of the cardiac lesions. Several observers felt that there was an interauricular septal defect and a superimposed rheumatic lesion of the aortic leaflets. One of them suggested a high ventricular septal defect with slight dextraposition of the aorta and aortic insufficiency.

AUTOPSY *J.H.H. No. 16613.* This was performed sixteen hours after death. The skeletal abnormalities were as described in the clinical history. The chief interest centered about the heart and great vessels.

The heart was tremendously enlarged; it weighed 840 grams, and almost completely filled the anterior mediastinum. The ascending aorta was greatly dilated. The epicardium and the coronary arteries were normal. The right auricle was dilated and filled with a post mortem blood clot. There was a large crescent-shaped opening at the upper margin of the foramen ovale which measured 2 cm. in length. The blood clot filled this aperture. Beneath it there was a smaller opening in the foramen ovale which measured 7 mm. in diameter. Both of these openings appeared to be of long standing and were rimmed by a cord-like edge of endocardium. The tricuspid ring was dilated; it measured 16 cm. The tricuspid leaflets were delicate. The right ventricle was hypertrophied and dilated; the

wall measured 10 mm. in thickness. The interventricular septum was intact. The circumference of the pulmonary valve measured 8 cm. The pulmonary artery was normal and showed a puckered scar at the site of the cord-like remnant of the obliterated ductus arteriosus.

The left auricle was so greatly dilated that the foramen ovale was incompletely closed. The two openings in the foramen ovale permitted free communication between the two auricles.

The mitral leaflets were delicate and the mitral ring was wide; it measured 13 cm. in circumference. The mitral valve was probably incompetent due to the great dilatation of the left ventricle. The wall of the left ventricle was hypertrophied; it measured 15 mm. The endocardium was thickened, and there were transverse ridges in the endocardium below the aortic valve.

The most marked changes were in the aortic valve and the ascending aorta. The aortic leaflets were huge; each measured 4 cm. from one commissure to the other. Though the cusps were delicate, the corpora Arantii were thickened. The entire circumference of the valve measured 13 cm. The coronary orifices were misplaced upward; each lay 6 mm. above the valve margin. Both orifices were slightly narrowed, but the lumina of the vessels were normal.

Immediately above the aortic valve there was a fusiform dilatation of the aorta (see Plate 6). The aortic ring measured 13 cm. in circumference and the ascending aorta reached a maximum circumference of 19 cm. and then tapered to 6 cm. just proximal to the origin of the innominate artery. The left subclavian and carotid arteries arose from a common orifice beyond which the aorta measured just 4.5 cm. in circumference. In the thoracic portion the aorta widened again to a circumference of 5 cm. The scar of the obliterated ductus arteriosus was quite prominent. Just above the sinus of Valsalva and extending into the ascending aorta the intima was thickened and wrinkled and pearly in appearance; the media and adventitia appeared to be normal.

The parenchyma of the lungs was normal. The bronchial mucosa was reddened. There were small, partly calcified tuberculous foci in both lungs. The liver weighed 1500 gm. and showed evidence of chronic passive congestion. The spleen was large and firm; it weighed 250 gm. The other organs were normal.

*On microscopic examination* the posterior halves of the eyes, obtained at autopsy, were normal. The corneas and lenses were not obtained. The hypophysis showed no lesion. Sections from the liver and spleen showed chronic passive congestion. There were some patches of edema in the lungs. There were thrombi in the small periprostatic and pericystic veins. The sections from the heart showed a few fibrous myocardial scars, not at all suggestive of healed rheumatic lesions. The mitral leaflets were delicate. The aortic leaflets were slightly thickened.

Examination of the *ascending aorta* revealed a remarkable condition. The smooth muscle of the media was distorted and formed irregular muscle bundles. Between these irregular muscle bundles there were numerous branching spaces which, in the majority of places, contained a gelatinous coagulum that stained blue with hematoxylin and eosin. In the largest spaces this material had dropped out

except for traces of it which were adherent to the margin. The media was honeycombed by smaller spaces. There were no distinct internal or external elastic lamellae. The medial elastic tissue was everywhere markedly distorted; the fibers were frayed and condensed in some places and in many areas they were lacking. The distortion of the media was further accentuated by numerous large blood channels which arose in the adventitia and penetrated into the media in an irregular fashion. The adventitia was in places slightly thickened and contained a few small foci of lymphocytes. Here and there the intima was thickened by layers of hyaline connective tissue (see Plate 7).

The abnormality of the media extended into the arch of the aorta. The thoracic and abdominal portions of the aorta were, however, entirely normal. Although numerous sections were made from the other arteries, the only additional abnormality was found in the pulmonary artery.

The *pulmonary artery* showed a slight abnormality similar to that found in the aorta but less extensive. In the media of the pulmonary artery there were tiny spaces in the inter-elastic tissue, some of which contained a faint amount of coagulum. However, no cysts or pronounced lesions similar to those in the aorta were found.

*Anatomical Diagnosis.* Arachnodactyly. Bilateral ectopic lentis; highly arched palate; thoracic and lumbar scoliosis; bilateral dislocation of the clavicles; bilateral hallux vulgus; hammer toes. Congenital fusiform dilatation of ascending aorta due to a malformation of the media. Great cardiac hypertrophy and dilatation. Incomplete closure of the foramen ovale. Chronic passive congestion of the liver and spleen.

## DISCUSSION

Two cases of arachnodactyly are reported in which there was extraordinary aneurysmal dilatation of the ascending aorta. In the first case the patient had been under observation since birth and was thought to have a congenital malformation of the heart. Clinically there was a loud systolic murmur, so loud as to be audible at a distance of two inches from the chest. In addition there was evidence of great enlargement of the left auricle and the left ventricle. The aneurysmal dilatation of the aorta was not detected either on fluoroscopic examination or by x-ray. The second patient was not seen until later in life and therefore the duration of the physical signs is not known. There was clinical evidence of great enlargement of the heart. The murmur was, however, much less intense. Although

some observers considered the possibility of interauricular septal defect, the enlargement of the left side of the heart was against this diagnosis. It is worthy of note that the x-rays of the barium-filled esophagus gave no indication of the fundamental malformation; namely, the enormous dilatation of the *ascending* arch of the aorta.

At autopsy the two hearts were almost identical. In both there was the marked cardiac enlargement. In each instance the left auricle was so greatly stretched that the valve covering the foramen ovale no longer completely closed it. In each the aortic ring was dilated and the coronary orifices displaced upward. In each there was tremendous dilatation of the proximal part of the aorta.

In both cases histological examination of the aorta revealed a malformation of the media. The abnormality involved both the muscular tissue and the elastic lamellae. The muscle bundles were rarefied and branched in a totally irregular fashion. Between the malformed muscle bundles there were large cystic spaces, which were filled with blue staining coagulum. Both the internal and external elastic lamellae were distorted. In some places the fibers were frayed or condensed; in many other places they were completely absent. The media was further distorted by numerous irregular blood channels which arose in the adventitia and invaded the media. There was no evidence of any inflammatory process except for the infrequent, small foci of lymphocytes in the adventitia. In the media, no cellular exudate was found and there was nowhere evidence of necrosis or degeneration.

The histological changes because of their location in the media and their cystic nature bring to mind the condition described by Erdheim (4) as "medial necrosis idiopathica cystica." But in Erdheim's cases the cystic changes in the media were primarily due to necrosis and senile degeneration and did not show the distortions of medial muscle bundles and blood channels such as occurred in our cases. A number of other investigators (Rottino (5, 6), Roberts (7), and Sailer (8)), have reported lesions similar to Erdheim's in cases of dissecting aneurysms.

Cystic changes in the media have been reported by a number of persons. Some investigators have thought the coagulum in the cysts to be mucoid. Costo-Florenz (9) found that mucoid material is normally present in the media of arteries of human embryos one to

three months of age and that this material normally disappears from the arterial wall with the growth of the embryo. He has, however, reported fifteen cases of adults with congenital hypoplasia of the elastica and musculo-elastica of the media with cystic changes in the aorta which he thought were due to a developmental disturbance. Harrison (10), Neuberger (11), and Wolff (12) have also reported cases in which there were cystic mucoid changes in the aorta; in each instance the patient showed some congenital abnormality but the only similarity to ours was the presence of mucoid-filled medial cysts. These reports taken together suggest that cystic changes in the media may be due to a congenital abnormality.

Our cases occurred in young persons with arachnodactyly and associated defects. There was no evidence of necrosis, cellular exudate, inflammation, arteriosclerosis or senile degeneration. The abnormality occurred in young adults and in each instance appeared to be due to an intrinsic structural defect in the media. The defect was most marked in the region of the ascending aorta, but in one case was also present in the thoracic aorta which in the gross appeared to be entirely normal. Therefore, we believe the condition represents a congenital maldevelopment. In both cases the abnormality of the media was so extensive in the ascending aorta that it caused an aneurysmal dilatation.

## SUMMARY

The occurrence of cardiac enlargement and aneurysmal dilatation of the ascending arch of the aorta is reported in two cases of arachnodactyly. The aneurysmal dilatation appeared to be due to a congenital malformation of the media.

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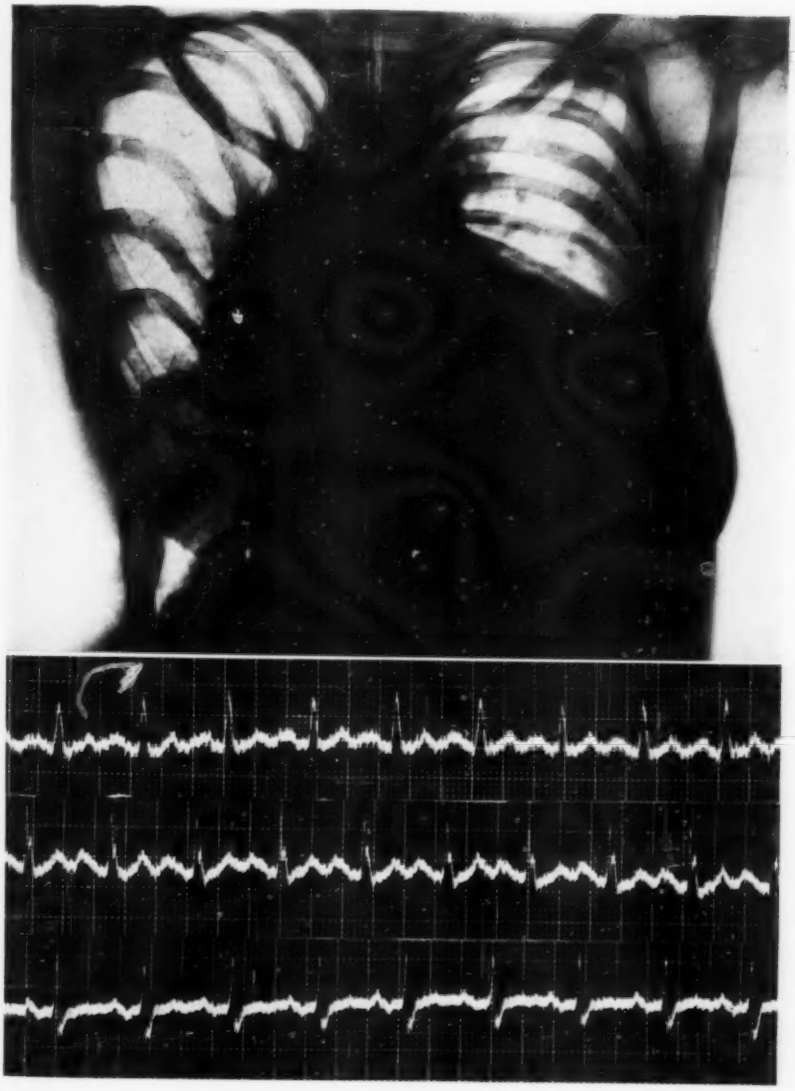
PLATE 1

CASE I. PHOTOGRAPH OF FEET AND LEGS

PLATE 2

CASE I. TELEOROENTGENOGRAM OF CHEST AND ELECTROCARDIOGRAM



## PLATE 3

CASE I. PHOTOGRAPH OF AORTA AND LEFT SIDE OF HEART

The great enlargement of the heart is seen to be due to the hypertrophy of the left ventricle. The aneurysmal dilatation of the aorta begins immediately above the widened aortic ring and extends through the ascending aorta. A small patch of superficial intimal roughening is shown at the upper portion of the specimen.

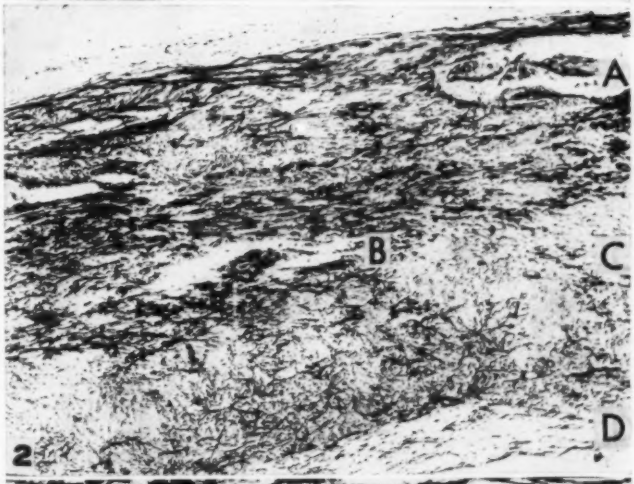
## PLATE 4

FIG. 1. Low magnification (×20) of H. and E. stain of the aorta of Case I, showing the general distribution of the cystic lesions in the media. Abnormally large blood channels can be seen to dip into the media from the adventitia.

FIG. 2. Higher magnification (×50) of elastic stain of the aorta of Case I. It shows A, an enlarged endothelial lined blood channel in the outer portion of the media, and B, a small cyst in the media. Rarefaction of elastic fibers can be noted in the inner zone of the media, C; and the normal intima is shown at D.

FIG. 3. Very high magnification (×190) of B in Fig. 2. The black lines are frayed elastic fibers, aggregated in patches and in places actually absent (as in the lower right portion of the section). The greyish material adhering to the margins of the cyst is blue staining coagulum.

1

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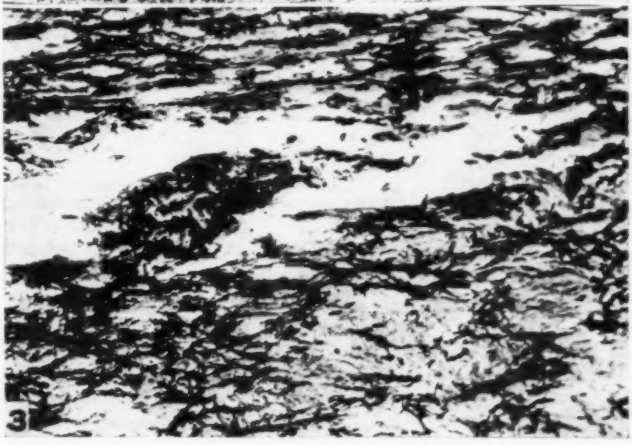

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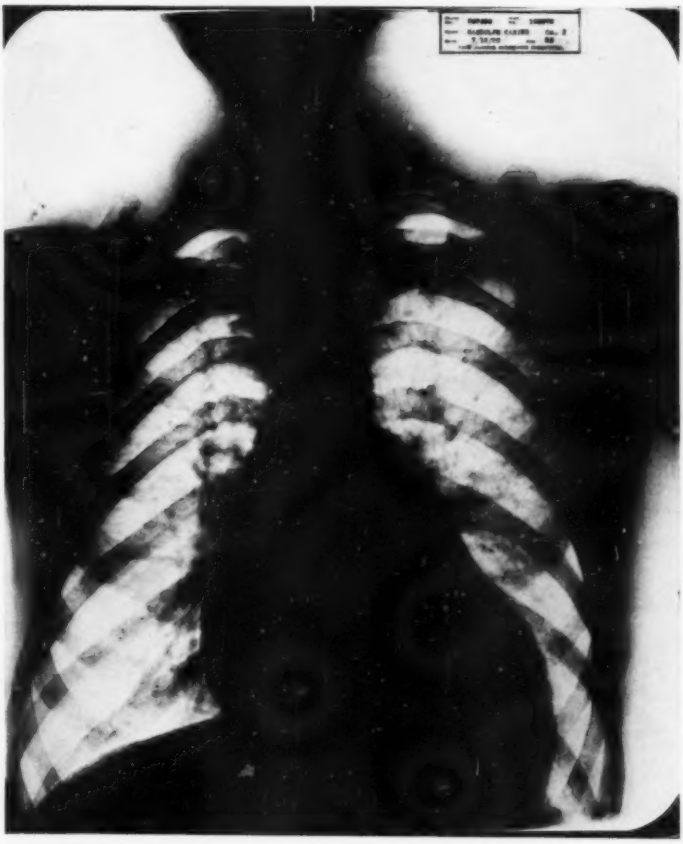
PLATE 5

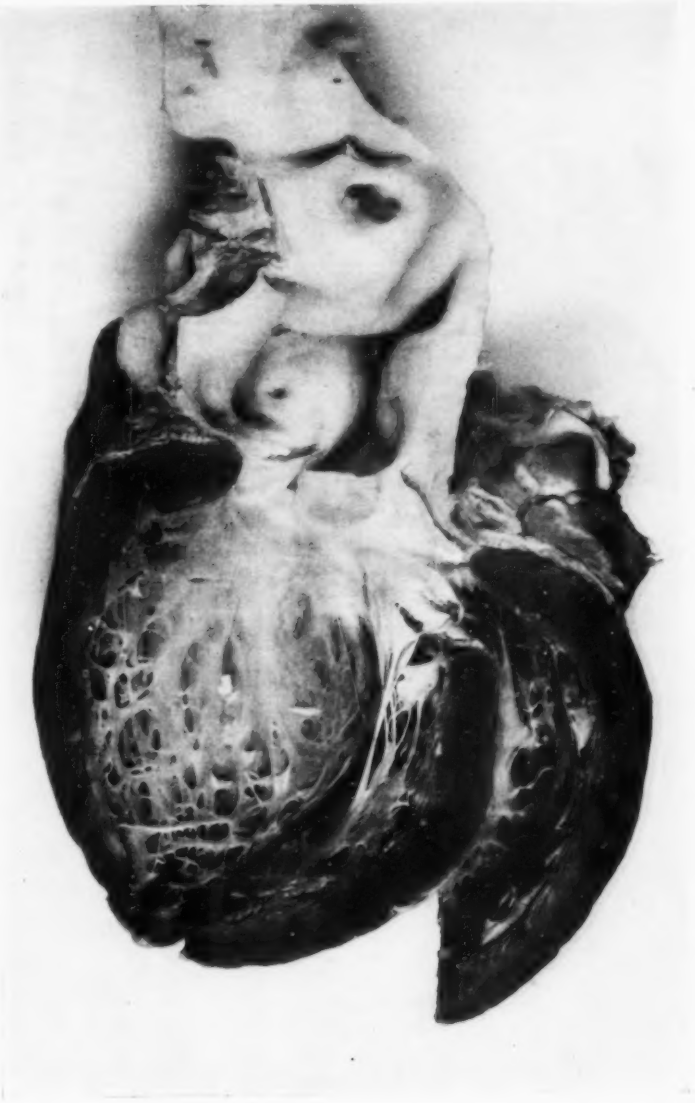
CASE II. TELEOROENTGENOGRAM OF CHEST



## PLATE 6

CASE II. PHOTOGRAPH OF AORTA AND LEFT SIDE OF HEART

The aneurysmal dilatation of the aorta is similar in position and extent to that in the first case. The orifice of the right coronary artery is plainly shown in its abnormal position high above the sinus of Valsalva.



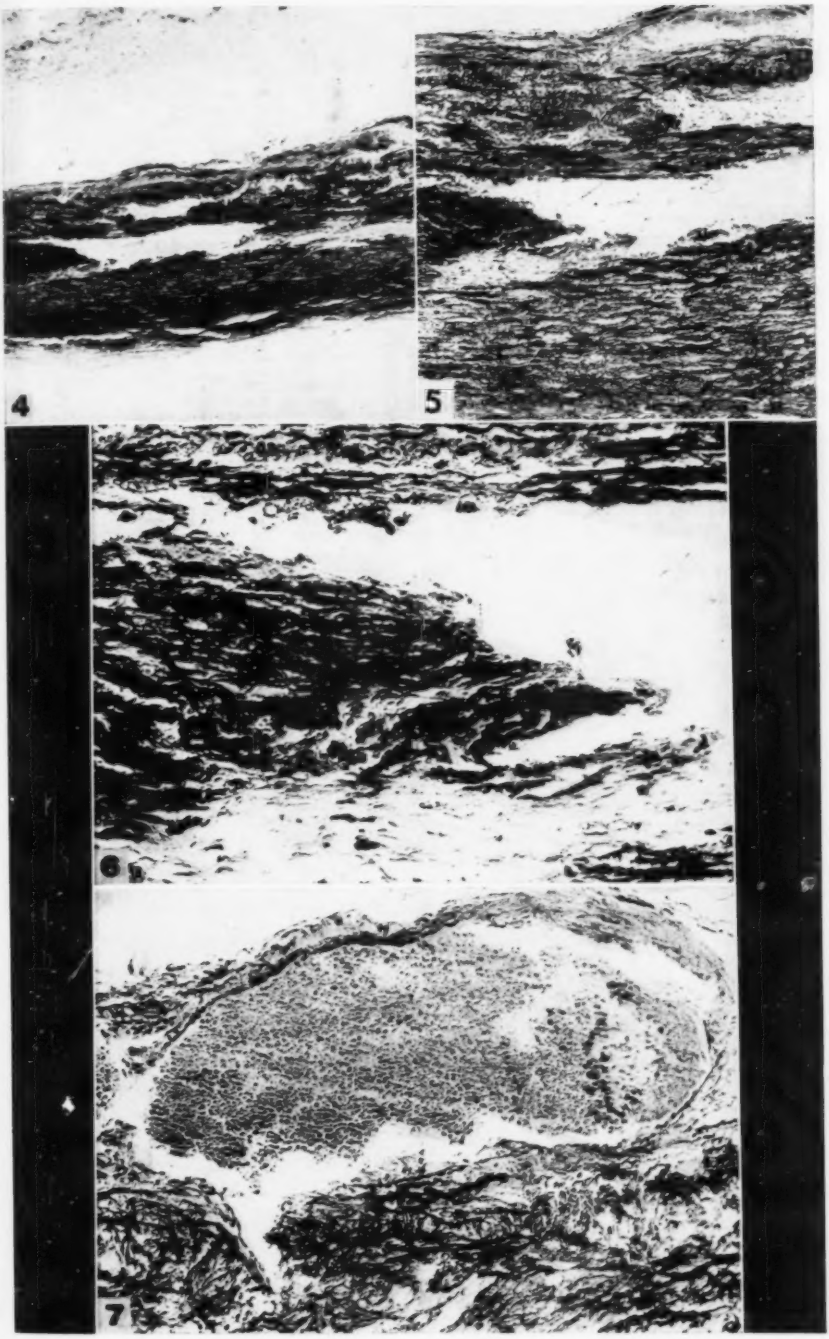
## PLATE 7

FIG. 4. Low magnification (×20) of elastic stain of the aorta of Case II, showing the distribution of the medial cysts, and the large abnormal blood channels in the outer portion of the media.

FIG. 5. Higher magnification (×50) of the above. The large blood channels are seen more distinctly in the upper zone of the media. At the left margin of the cyst, aggregated elastic fibers are seen; below the cyst there is rarefaction of elastic fibers. A slight remnant of coagulum is visible in the cyst.

FIG. 6. Very high magnification (×190) of the left margin of the above cyst, showing the irregularity in the direction of the elastic fibers, and a zone of complete loss of elastic tissue.

FIG. 7. Very high magnification (×190) of a large medial blood vessel in the above, lined with endothelium and filled with blood cells. A few frayed elastic fibers can be seen in the adjacent media.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# EVERSION AND HERNIATION OF THE CORPUS LUTEUM

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In a recent paper on the ovary of the fox, Pearson and Enders (1943) illustrate a remarkable case of eversion of a corpus luteum in which that structure, normally a thick-walled spheroidal sac in the fox as in most other animals, is completely everted. In the section illustrated by the authors (fig. 15, pl. 4, of the paper cited) the lutein tissue lies on the surface of the ovary like a pocket turned inside out. This specimen illustrates a variation of the form of the corpus luteum which occurs as an anomaly in some species, while in a few animals, including certain insectivores and apparently one of the bats, it is constant and normal. To mention first the cases in which eversion of the corpus luteum is an abnormality, Mossman (1937) reports having seen, in four ovaries of the pocket gopher, *Geomys bursaria*, corpora lutea lying like plaques on the ovarian surface. Stratz (1898) illustrates an example of what he calls exstrophy of the corpus luteum in *Tarsius spectrum*, in which the lutein tissue projects from the ovary in a fungiform mass. I do not recall having seen reports of eversion of the corpus luteum in the human ovary. I have, however, seen in the rhesus monkey three cases of herniation and more or less complete eversion of the corpus luteum.[1]

*Case 1.* During the course of an exploratory operation on monkey C.187, a corpus luteum was seen which was so widely everted that about two-thirds of its tissue stood outside the ovary, forming a brilliant deep red cauliflower-like crater 7 mm. in diameter (usual size of whole ovary is about 6 x 8 x 11 mm.). The appearance of this everted corpus luteum was so different from anything previously seen as to excite the wonder of the experienced experimental team and even to evoke the conjecture that it might be a tumor. Since it was necessary for purposes of the experiment to leave the ovary intact, a biopsy was not done. At autopsy 5 weeks later, the corpus luteum, now regressive and much reduced in size, was

[1] The author's experiments on monkeys were supported, at the time when these observations were made, by a grant to the University of Rochester by the John and Mary R. Markle Foundation.

found to have settled down into the ovary and its once wide-open crater was covered by an adhesion to adjacent peritoneal tissue.

*Case 2.* During an exploratory operation on monkey C.223, a similar corpus luteum was seen, having a bright red mushroom-shaped mass, 5 mm. in diameter, with a central depression. In this case the corpus luteum had evidently herniated through a rent in the tunica albuginea slightly narrower than the exposed mass, leaving only a small part of its substance within the original site of the follicle. A biopsy was avoided because of the program of the experiment. At autopsy 9 weeks later the regressing corpus luteum, now a corpus aberrans (see Corner, 1942), had withdrawn almost but not quite completely within the normal limits of the ovary, leaving a wide and still slightly projecting crater (fig. 2).

*Case 3.* Monkey C.148 underwent a twin ovulation, forming two corpora lutea, one of which was quite normal. The other protruded from the ovary, forming an immense bright-red crater. The ovary was removed and sectioned. By reconstruction from serial sections it was found that about two-fifths of the bulk of the corpus luteum lay exposed on the surface of the ovary. The plane of section is not entirely favorable for illustration, but figure 3 gives a fairly adequate idea of this corpus luteum.

As the reader will perceive, these three cases in the monkey may all be considered examples of herniation of the corpus luteum through its stigma (point of rupture of the follicle). Hartman (1939) has pointed out that in the rhesus monkey the size of the orifice created at the time of ovulation varies from a pin point to a couple of millimeters in diameter. When the orifice is in the larger range, there is always a little protruding crater of corpus luteum tissue. Such a mass, called "Propf" by the Germans, is usual in the human corpus luteum and in that of many other species. The three monkey cases cited above show that at times the tearing of the follicle wall is even greater, permitting the extrusion of two-fifths, two-thirds or more of the corpus luteum tissue. No doubt pressure exerted by other structures, such as the twin corpus luteum in Case 3 above, will promote the herniation. When the follicle wall is ripped wide open, complete eversion will occur, as in the case of Pearson and Enders. In this case the smooth muscle cells in the follicle wall will assist in the mushrooming of the luteum tissue. The diagram, figure 1, illustrates schematically the several stages of this process from the normal to the completely everted corpus luteum.

Mossman, when discussing his cases in *Geomys*, cited above, has already suggested that the eversion results from extreme width of the

rupture-perforation of the follicle wall. Such an explanation fits also the extraordinary case of the elephant shrew (*Elephantulus myurus jamesoni*) a small South African insectivore described by Van der Horst and Gillman (1942). In this creature eversion of the corpus luteum is normal and constant. At the time of ovulation almost half the follicle wall (the part which is exposed on the surface of the ovary) is thinned out and is destroyed when the follicle ruptures. This leaves the bared granulosa cells to project from the ovary, generally forming an exposed, slightly convex surface of lutein tissue. The exact form of the corpus luteum thus formed differs, however, according to the space available and the obstacles encountered, and it assumes all gradations of form between that of a mushroom and a dumbbell, just as in our three cases in the rhesus monkey.

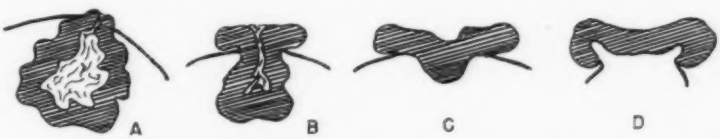


FIG. 1. Diagram illustrating various forms of the corpus luteum discussed in this paper, as if seen in sections: A, normal corpus luteum of rhesus monkey. B, partial extrusion and eversion, as in Case 3 (monkey C.148). C, marked eversion, interpreting observation made in Case 1 (monkey C.187). D, extreme eversion, as in the fox reported by Pearson and Enders.

In two species of insectivores belonging to the family of *Centetidae*, namely the tenrec (*Ericulus*) and *Hemicentetes*, described by Strauss (1939) the granulosa of the follicle forms a solid mass, without a cavity. After the expulsion of the ovum the corpus luteum protrudes widely from the ovary and to a certain extent spreads outward like the everted corpus luteum of the elephant shrew.

The inclusion of the bat *Rhinolophus* among the animals with normally everted corpora lutea rests upon a brief statement by Van Beneden (1901).

It seemed to the present writer worth while to test by actual experiment the rather obvious hypothesis, which has occurred to all who have written on this subject, that excessive width of the rupture point is a cause of herniation and eversion of the corpus luteum. A female

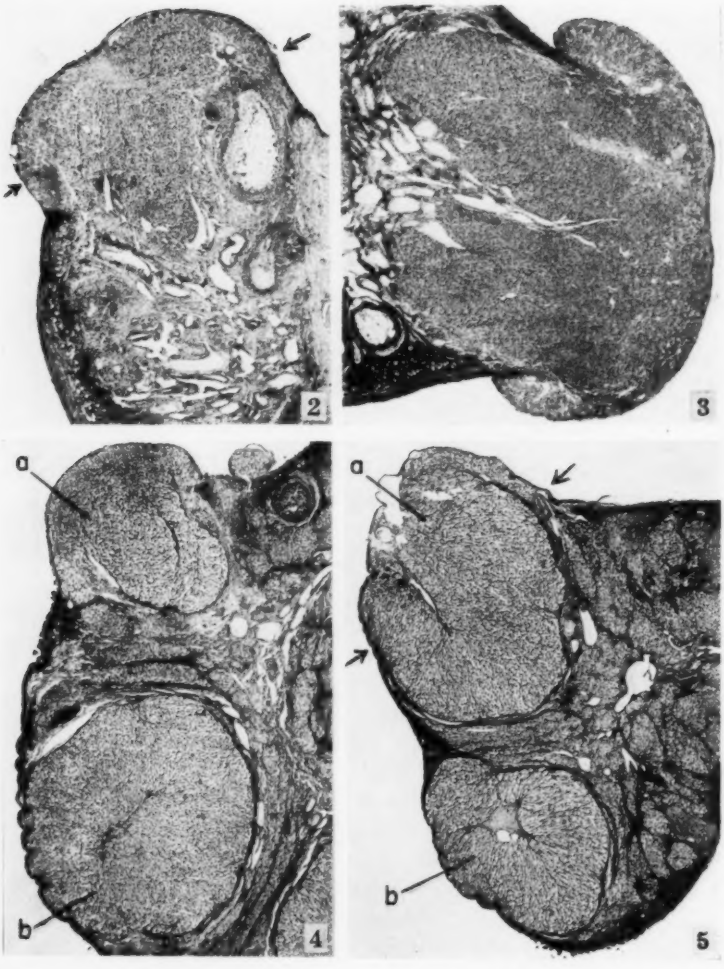


FIG. 2. Everted corpus luteum in retrogression, Case 2 (monkey C.223). Arrows indicate the extent of the protrusive lutein tissue. × 15.

FIG. 3. Section through partially everted corpus luteum, Case 3 (monkey C.148) × 15.

FIG. 4. a, corpus luteum of rabbit everted as result of incision of the follicle. b, normal corpus luteum of same age. × 15.

FIG. 5. a, corpus luteum of rabbit partially everted as result of incision of the follicle. b, normal corpus luteum of same age. × 15.

rabbit was mated at 7:40 a.m. and at 5:30 p.m. of the same day an ovary was exposed under ether anesthesia. As expected, the ovarian follicles were large and ruddy and were undoubtedly about to rupture. Ten ripe follicles were counted. Five of these were each cut wide open with a sharp iridectomy knife. The cut was deep enough to divide all that part of the follicle wall that projected above the general level of the ovary and to cut slightly into the ovarian substance. At autopsy 9 days later the 5 corpora lutea which formed at the sites of the incised follicles all showed various degrees of herniation and eversion (figs. 4, a and 5, a) whereas the follicles which were left intact had formed no more than the usual small craters (figs. 4, b and 5, b; but note that the points of rupture of these normal corpora do not appear in these sections).

*In conclusion,* the altogether striking and unfamiliar appearance of the herniated and everted corpus luteum, as seen in the monkey, should be emphasized. The large, velvety, vividly red excrescence thus formed stands out with startling intensity. Since this condition of the corpus luteum results, as we have seen, from variations in the degree of laceration of the follicle at the point of rupture, there is every reason to expect that it will occur sometimes in the human ovary. Seen for the first time at the operating table, it might impress itself upon an unwary surgeon as some sort of fulminating ovarian tumor and thus cause an unnecessary ablation of the ovary.

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# THE RELATIONSHIP OF CHEMOTHERAPY IN PNEUMONIA TO THE PERSISTENCE OF PNEUMOCOCCI[1]

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This study has been conducted for the purpose of determining the effect of sulfonamide drugs, used for the treatment of pneumonia, on the length of time pneumococci are carried in the nasopharynx. Since pneumococci retained in the pharyngeal or oral secretions of patients convalescent from penumonia undoubtedly serve as one source of spread of the organisms, it is of interest to estimate the extent to which chemotherapy administered for treatment of the acute phase of the infection affects the ultimate persistence of the organisms. For this purpose, cultures of the pharynx have been taken at frequent intervals during the patient's course in the hospital and the results have been correlated with the duration of specific sulfonamide therapy.

Persistence of pneumococci in the nasopharynx during convalescence from pneumonia has been studied by several investigators in patients who received no specific therapy and, also, to a more limited degree, in cases treated with antipneumococcus serum. Dochez and Avery (1) studied the problem with respect to the persistence of the homologous type of organism in cases of pneumonia due to pneumococcus Types I, II, and III. They found that the length of the convalescent carrier state varied from 10 to 90 days after the onset of the illness, and concluded that in some instances the types of infecting pneumococci may be carried by patients for a considerable period of time after recovery. The authors stressed the importance of the convalescent carrier in the continued spread of the disease.

Stillman (2) studied 53 cases of lobar pneumonia due to Types I, II, and III pnemococcus. In his results, the shortest carrier period, when measured from the onset of the disease, was found to be 7 days,

[1]This investigation was supported by funds contributed by Mr. and Mrs. Henry R. Luce.

and the longest, 85 days. He emphasized the significance of delayed resolution or the occurrence of some complicating infection of the respiratory tract in association with long persistence of the organism.

Avery, Chickering, Cole, and Dochez (3) found a persistence range of 7 to 90 days in 15 cases of pneumonia due to Types I, II, and III pneumococci. The authors placed the average time of disappearance at 3 to 4 weeks and considered pulmonary complications responsible for protracted carrier states.

Jacobson (4) studied 9 cases of pneumonia due to Types I and II pneumococci and found the range of persistence to be from 8 to 150 days, with the findings for each type approximately the same.

Christie (5) examined the sputa of 24 cases of pneumonia, shortly after crisis, and repeated the examination when the patients were ambulatory, and also just before discharge. Only 6 out of the 24 were without pneumococci during the convalescent period. Type I pneumococcus persisted in 6 cases out of 14 and Type II in 9 out of 10.

Cruickshank (6) followed 250 cases of Types I and II pneumococcus pneumonia during convalescence and for several months after discharge from the hospital. In his series the proportion of carriers fell from 60 per cent immediately after crisis to 35 per cent 3 weeks later. Complications caused a more protracted carrier state. A number of these cases were followed at 2-month intervals after dismissal from the hospital. 38.4 per cent of 52 patients still carried their original type 2 to 4 months later, and 22.4 per cent of 49 retained the homologous type of organism for as long as 6 months. He considered the chronic carrier a possible source for the dissemination of the infection, and believed that patients recovered from pneumonia make up a large portion of this group.

Pedersen (7) studied by examination of sputum or throat culture 73 hospital patients with pneumococcus pneumonia. The most seriously ill patients received type-specific antiserum. Some lost the pathogenic pneumococcus within a few days, whereas others were carriers for weeks or months. 50 per cent retained the original strain of pneumococcus for 8 days following admission to hospital and 25 per cent for 17 days. $33\frac{1}{3}$ per cent were discharged from the hospital still harboring the type of organism responsible for their infection.

From an estimate of the reports mentioned it appears to be ap-

proximately correct to conclude that about 40 per cent of patients lose the infecting pneumococci during the early phase of recovery from pneumonia, and that an additional 25 per cent lose them within the subsequent three weeks. In approximately $\frac{1}{3}$ (33 to 35 per cent) the organisms endure for varying additional periods of time up to several months. In the latter group the persistence of pneumococci has been frequently ascribed (2, 3, 6) to the presence of chronic pulmonary disorders that have been present after the acute pneumonic state has subsided. Among the patients, however, who completely recovered from pneumonia and who retained no clinical evidence of chronic pulmonary disease there have remained a group of presumably healthy carriers. Whether or not the persistence of pneumococci under such circumstances may be accounted for on the basis of mild chronic infection of the lymphoid tissue of the nasopharynx or of sinusitis has not been definitely excluded. Webster (8) emphasized the significance of the occurrence of chronic infection of the upper respiratory tract in relation to the persistence of pneumococci in carriers.

The results contained in this report were derived from repeated cultures made on patients who were treated with sulfonamide drugs. By comparing the data obtained with the reports previously reviewed the attempt has been made to estimate what effect, if any, the use of chemotherapy has had upon the ultimate disposition of pneumococci in treated cases.

## METHODS

Throat cultures were taken at frequent intervals from the time of admission to the date of discharge. A final culture was taken in most instances on the day of discharge, or, in case of fatal termination, one to two days prior to death. Even if the culture became negative during either the active or convalescent stage of the disease, subsequent examinations were made until the patient left the hospital.

The procedure consisted of swabbing the throat vigorously, placing the swab in Avery's dextrose blood broth medium, and incubating at 37 degrees centrigrade for four to six hours. 0.5 cc. of this culture was then inoculated into the peritoneum of a white mouse. Upon the death of the mouse, usually within 24 to 48 hours, a culture of the heart blood was taken and pneumococci thus isolated were typed by the Neufeld method. Not infrequently a positive Quellung reaction was obtained from the original dextrose blood broth culture following incubation. In such instances, further identification by mouse inoculation was considered un-

necessary. Mice which survived and appeared healthy at the end of 7 days were discarded.

## OBSERVATIONS

The present series consisted of 47 cases of lobar pneumonia treated on the wards of the Third (N. Y. U.) Medical Division of Bellevue Hospital. There were 9 cases of Type I pneumococcus pneumonia, 6 cases of Type II, 8 cases of Type III, 4 of Type V, 8 of Type VII, 3 of Type VIII, 2 of Type XXII, and one each of Types IX, XIV, XV, XVIII, XXV, XXVIII, and XXXIII. 37 cases were treated with sulfapyridine, 2 with sulfathiazole, 6 with sulfapyridine and sulfathiazole and 2 received sulfapyridine and serum.

In correlating the period of sulfonamide administration with the bacteriological findings, the cases were found to fall into two groups. Group I constituted the patients in whom the original type of pneumococcus disappeared either during sulfonamide therapy or within 2 days of its discontinuance. Since the drug is, as a rule, almost completely eliminated from the blood within 48 hours of the cessation of administration, any effect on the organisms persisting after this period would appear to be negligible. The other group consisted of the patients in whom pneumococci were found after the drug had been eliminated from the body.

21 cases belong in the first group. In 17 of them, recovery was prompt and complete. In 3, there were pulmonary complications secondary to the pneumococcus infection.

One died despite adequate chemotherapy and negative blood and throat cultures, probably from the debilitating effects of malnutrition, avitaminosis and generalized and cerebral arteriosclerosis. In 6 of the patients of Group I, attempts to isolate the pathogenic pneumococcus were not successful, except for the culture taken on the day of admission. In 6, the organism was not recovered after the second day of therapy, in 3 after the third, in 2 after the fourth, in 3 after the fifth and in 1 after the seventh. The average period of therapy for Group I was 6.4 days and the average total dosage of drug was 31.3 gms. per patient.

Group II comprises the patients who retained the original type pneumococcus in the pharynx, both during the period of therapy and

also for longer than 2 days after therapy had been discontinued. There were 26 cases in this group. 21 had uneventful courses, while 5 were complicated. In 18, the last culture taken before they left the hospital was positive, whereas, in the remaining 8, there was disappearance of the infecting bacteria before discharge. The number of days of treatment of Group II, and the total amount of drug received averaged 5.9 days and 28.5 gms., respectively per patient. These average figures are comparable to those for Group I.

Considering both groups as a whole, 61.7 per cent lost the homologous type pneumococcus while under observation in the hospital, 44.7 per cent during the period of therapy and 17.0 per cent after

TABLE I

*Relation of chemotherapy to carrier state in complicated and uncomplicated cases*

| CASES | CULTURES WHICH BECAME NEGATIVE DURING PERIOD OF CHEMOTHERAPY | | CULTURES WHICH BECAME NEGATIVE AFTER PERIOD OF CHEMOTHERAPY | | CULTURES WHICH WERE POSITIVE AT TIME OF DISCHARGE FROM HOSPITAL | |
|---|---|---|---|---|---|---|
| | No. of cases | Per cent total | No. of cases | Per cent total | No. of cases | Per cent total |
| Uncomplicated..... | 18 | 38.3 | 6 | 12.8 | 15 | 31.9 |
| Complicated..... | 3 | 6.4 | 2 | 4.2 | 3 | 6.4 |
| Total..... | 21 | 44.7 | 8 | 17.0 | 18 | 38.3 |

cessation of treatment. 38.3 per cent retained the organism throughout the entire period of hospitalization. Therefore, in 55.3 per cent the bacteriological findings, as determined by throat cultures, appeared to be uninfluenced by the drug, as compared to 44.7 per cent in which the disappearance of the pathogenic bacteria coincided with the administration of sulfonamide compounds. Table I shows the above data in composite form, with percentage figures relative to the entire series.

Pulmonary complications were encountered in this series in 8 cases. Delayed resolution occurred in 4, sterile effusion in 3, and lung abscess in 1. Pneumococcus types recovered from these cases were II, III (2 cases), V, VII, IX, XV, and XXXIII. Of the 3 patients with complications who lost the homologous type pneumococcus during the period of therapy, it is interesting to note that in each one heter-

ologous types of pneumococcus appeared later. The newly acquired types were present for varying periods of time during the stage of complication.

Table II shows the length of time in weeks that the homologous type pneumococcus was present in the pharynx of those patients losing

TABLE II

*Duration of positive cultures in patients whose cultures became negative under observation*

29 cases

| TIME IN WEEKS MEASURED FROM DAY CHEMOTHERAPY STARTED | NUMBER OF CASES | |
|---|---|---|
| | Uncomplicated | Complicated* |
| 1 | 24 | 5 |
| 2 | 4 | 3 |
| 3 | 0 | 2 |
| 4 | — | 2 |

*The complicated cases which were positive beyond the 4th week did not show negative cultures until the 5th and 8th weeks respectively.

TABLE III

*Known duration of positive cultures in patients whose cultures were positive when discharged from observation*

18 cases

| TIME IN WEEKS MEASURED FROM DAY CHEMOTHERAPY STARTED | NUMBER OF CASES | | | |
|---|---|---|---|---|
| | Uncomplicated | | Complicated | |
| | Remaining in hospital | Discharged | Remaining in hospital | Discharged |
| 1 | 13 | 2 | 3 | 0 |
| 2 | 7 | 6 | 3 | 0 |
| 3 | 3 | 4 | 1 | 2 |
| 4 | 1 | 2 | 1 | 0 |
| 5 | 0 | 1 | 1 | 0 |
| 6 | — | — | 1 | 0 |
| 7 | — | — | 0 | 1 |

the organism while in the hospital. From this table it can be seen that among the great majority of the uncomplicated cases which became negative, the pathogenic types of pneumococcus were lost during the first week, whereas in the 5 instances associated with complications 2 had positive cultures for periods up to 5 and 8 weeks.

It is interesting to note that among the cases which lost the original

infecting penumococcus, in 7 instances a heterologous type was acquired during convalescence. Three of these, as previously mentioned, were in the group having pulmonary complications, while the other 4 recovered promptly in spite of the acquisition of another type of pneumococcus. In not one of the cases was the homologous type organism recovered after the appearance of the new type. Only one patient acquired more than a single heterologous type. Types VI, VIII, IX, XI, XVII, XXIII and 2 unclassified strains were isolated from these 7 patients following the apparent disappearance of the pneumococcus present on admission to the hospital. Goodwin and Finland (9) noted in occasional cases that new types appeared during the course of treatment and after the original type could no longer be found.

Table III concerns the 18 cases in which there were persistently positive cultures until discharge and demonstrates the period of positivity while under observation. Variations in the periods of observation were caused by differences in the length of stay of the patients during convalescence in the hospital.

## DISCUSSION

In 55.3 per cent of this group of patients sulfonamide therapy administered during the acute phase of the infection had no effect on the pneumococcus carrier state. The remainder of the group—44.7 per cent—lost the homologous type pneumococcus during the period of treatment. These findings correspond to the estimated 40 per cent of untreated and serum treated patients who lost their organism early in the course of their disease. In the present study 38.3 per cent of the 47 cases had positive cultures at the time of discharge from the hospital. This figure agrees closely with the 33 per cent of patients, as estimated from the literature, who retain the organism for several months, and the 33 per cent in Pedersen's group (7) who left the hospital carrying the pneumococcus responsible for the infection. From the above data it would seem reasonable to conclude that specific chemotherapy has effected no significant reduction in the number of persons who become pneumococcus carriers following lobar pneumonia.

Goodwin and Finland (9) found in patients treated with sulfona-

mide drugs that in about half the cases pneumococci disappeared from the sputum or throat cultures within 48 hours after the drug was started and in an additional 30 per cent they could not be found after 3 to 10 days.

As has been pointed out by Stillman (2), Avery, Chickering, Cole, and Dochez (3), and Cruickshank (6) pulmonary complications are frequently responsible for prolonged persistence of the infecting type pneumococcus in the pharynx and mouth secretions. Observations in this study tend to confirm this impression even though chemotherapy was employed.

Heterologous types of pneumococci were recovered in 7 patients during convalescence. In each instance the homologous type of organism had disappeared as estimated by at least one negative culture prior to the isolation of the new type. Subsequently the homologous type was not found during the patient's stay in the hospital. Whether or not the disease producing type temporarily overgrew the non-disease producing type during the acute phase of the illness cannot be definitely determined. Since, however, one strain disappeared and another became demonstrable it is interesting to consider the factors which differentiate the carrier qualities of the two strains. Studies now in progress deal with this problem.

In evaluating the technique employed it should be noted that in 13 instances one or more negative cultures were followed by the successful reisolation of the homologous type. There were 10 instances in which the infecting type of pneumococcus could not be isolated on one occasion, only to be recovered on the next culture. In 3 cases 2 successively negative cultures were followed by a positive one. Stillman (2) has made similar observations. The results emphasize the limitations which are placed upon the interpretation of a single negative culture.

Additional investigations will be subsequently reported which deal with chemotherapy as a means of affecting the carrier state in convalescence and in normal persons.

## SUMMARY

1. The persistence of pneumococci in the upper respiratory passages of 47 cases of lobar pneumonia treated with sulfonamide compounds

has been studied by making repeated throat cultures during the period of hospitalization.

2. 44.7 per cent of the patients lost the pathogenic type pneumococcus during the administration of the drug. 17.0 per cent lost the pathogenic pneumococcus after the drug had been discontinued, but before discharge from the hospital. 38.3 per cent left the hospital carrying the pneumococcus responsible for their disease.

3. Pulmonary complications were frequently associated with a prolonged carrier state.

4. Heterologous type pneumococci were recovered in seven instances following the apparent disappearance of the pneumococcus type isolated on admission to the hospital.

5. In so far as comparison with the findings of the earlier literature on the carrier state following pneumonia is possible, it would appear that the convalescent carrier rate has not been significantly reduced by the routine use of sulfonamide compounds in the treatment of pneumococcus pneumonia.

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# THE NUCLEINATE-LIKE ACTION UPON THE WHITE BLOOD CELLS OF THE ETHER INSOLUBLE FRACTION OF LIPOIDS FROM BEEF BRAINS[1]

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The ether insoluble fraction of brain lipoids is known as "protagon," and represents a fairly constant mixture of cerebrosides and sphingomyelins (9). The effects upon the blood and tissues from repeated intravenous injections of rabbits with this mixture have been reported (14). Serial counts of the white blood cells over twenty-four hour periods following individual injections in the course of those experiments revealed such characteristic curves that studies following single injections were elaborated into the present series. It seemed that these could be presented more simply by separate report, than by inclusion in the report concerning the other reactions to protagon.

## EXPERIMENTAL PROCEDURES

The method of extraction of the ether insoluble fraction of brain lipoids has been described (14). The dried ether insoluble residue was dissolved in a warmed mixture of equal parts of ethyl alcohol and chloroform and filtered through fine paper. The filtrate served as the stock solution used in the preparation of the emulsions for injection. It became slightly turbid on cooling and was always shaken before use. It gave a negative test for the imidazol group and for pentose (determinations of the olive green reaction with orcinol [Bial's reagent] by means of the Cenco-Sheard spectrophotelometer established the absence of the absorption bands characteristic of the reaction between pentose and Bial's reagent[2]). This material was used for nine rabbits (nos. 4–6 and 8–10 inclusive, 13, 32 and 33). With the exception of rabbits 32 and 33, these animals were included in the report of the tissue reactions to injections of the same material (14).

While it was believed that solution and filtration from the alcohol-chloroform mixture would have served to remove non-lipoid contaminants that might have

[1] Presented before the American Association of Anatomists, Chicago, April, 1941. *Anat. Rec.*, **79:** Supp. 59, 1941.

[2] The author is very grateful to Dr. Ann S. Minot, Department of Pediatrics, Vanderbilt Medical School, for her assistance in these determinations.

been carried along with the ether insoluble residues, one portion of the stock solution was subjected to the process described by MacLean (8) for the removal of water soluble impurities from lecithin. This portion was dried over a water bath, and emulsified in distilled water. Sodium chloride was added and the emulsion was cooled to 40°C. Cooled acetone was added and the precipitate was allowed to settle in the cold. The supernatant fluid was decanted, and the precipitate was washed several times with fresh cold acetone. It was then re-dissolved in water and the process repeated. The final acetone insoluble material was dried in air and stored in a dessicator, from which it was used directly for the emulsions. This material was used for rabbits 34 and 42.

Fresh emulsions were prepared for each injection. The required amount of the filtered stock solution was dried over a water bath, emulsified in 5 per cent glucose in proportions of 5 per cent and sterilized two hours in a steam sterilizer. The dry material which had been extracted for water soluble impurities was emulsified and sterilized in the same way. Control studies were carried out after injections of 5 per cent glucose, sodium nucleinate, and egg lecithin, and diurnal counts were also made.

The rabbits used throughout these studies were healthy, adult, non-pregnant females. All were kept under similar conditions. They were given a liberal diet of oats, rabbit pellets (Purina) and mixed greens with water and salt ad libitum. They were kept in separate, large cages, and were either taken in and out of these for the counts, or were allowed to hop about the laboratory during the period of counting. They were animals that had long been familiar with handling by the laboratory personnel and with the procedure used for blood counts, and they rarely exhibited any disturbance incident to the repeated examinations necessary for these studies. They were allowed food freely between the individual counts of any given experiment, and they frequently munched even while the blood was being drawn. They were sufficiently acclimated not to require restraint for this procedure.

Two to three control counts were made at hourly intervals preceding any given injection that was to be followed serially. Twenty-one gauge Vim needles were used, and were sharpened frequently in order to produce the minimum of trauma. The injections were given slowly in the ear veins over a period of three or more minutes. With the exception of rabbit 32, the animals never exhibited untoward reactions under those conditions. The blood counts were then followed for six hours at hourly intervals, beginning 15 to 30 minutes after the injections; and then at two hour or longer intervals, as indicated, for another six to eighteen hours. They were usually not followed longer than twenty-four hours after an injection, since another injection of the experimental lipoids was then due in most instances.

Serial studies of the red blood counts were carried out in only a limited number of cases. The blood was always drawn concomitantly with that for the white counts.

Trenner automatic pipettes and Levy Hausser counting chambers were used for all counts. The blood was drawn from a freely flowing puncture of the mar-

ginal veins of the ears. All samples were drawn in triplicate. The counts were made in duplicate with the third pipette held in reserve for instances when the duplicate counts disagreed. All data represent absolute numbers based upon the average of the total counts. Turk's solution was used for the white counts and Hayem's, for the red counts.

The differential white blood counts were made upon 200 cells in supravital smears stained with neutral red only. All qualitative observations of both red and white cells were made from the supravital smears.

## EXPERIMENTAL DATA

In the case of rabbits 4–6, 8–10 and 13, which received repeated injections of the mixture of ether insoluble lipoids (14), the dosages were increased gradually from 0.05 gm. to levels of from 0.5–0.7 gms. daily. Serial counts of the blood following individual injections of these rabbits were not begun until the daily dosage was 0.5 gm. Rabbits 32 and 33 were therefore given single injections of the same material in amounts of 0.5 gm. and 0.1 gm., respectively. The portion which had been extracted for water soluble impurities was also given as single injections in amounts of 0.2 gm. and 0.15 gm., respectively, to rabbits 34 and 42. Charts 1–4 represent counts following individual injections of rabbits which were receiving daily injections, and chart 5, the counts following a single injection of the same material after extraction of water soluble impurities. Table I presents the data on the remainder of the rabbits which received protagon.

The reaction of the white blood cells to an individual injection of this mixture of lipoids was the same qualitatively in every instance, and varied only in intensity. Regardless of the level of the pre-injection counts, the injections were followed by leucopenia within half an hour, this being due to a decrease of granulocytes within the same interval, followed by a decrease of lymphocytes within one half to two hours of the injection (cf. charts 1 and 2). The neutropenia was quickly succeeded by an increase in polymorphonuclear cells, beginning from one to four hours after the injection, reaching a peak in from two to twelve hours after the injection, and continuing anywhere from eight to more than twenty-four hours after the injection. The increase in granulocytes was sufficiently intense to produce leucocytosis, despite a continued reduction of lymphocytes which continued for eleven or twelve hours from the time of the injection. The lympho-

cytes then gradually returned to the pre-injection level, or higher. In general, the monocytes paralleled the lymphocytes. In rabbits 34 and 42, which were given single injections of protagon, the counts were

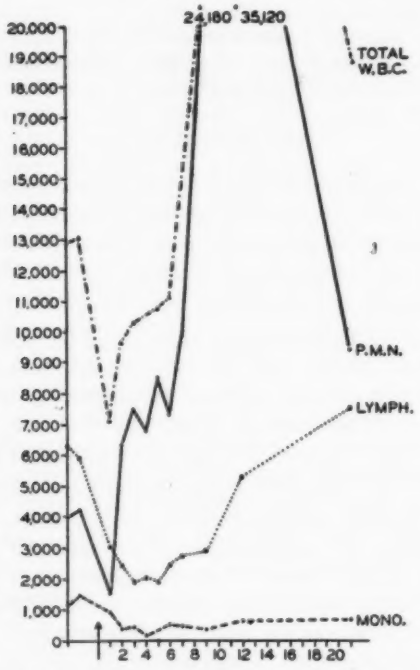


CHART 1. Rabbit 4. Counts of white blood cells following injection of 0.5 gm. of protagon on the 49th day after daily injections were started. The intensity of the reaction is estimated as ++++.

In all of the charts the arrows point to the time of injection, the abscissae represent hours in relation to the time of injection, and the ordinates represent absolute numbers of blood cells. One division of the ordinates is equivalent to 1,000 white blood cells and 1,000,000 red blood cells.

continued longer than in the others; and in those two instances, both the lymphocytes and the monocytes increased considerably above the pre-injection levels at about twenty-four hours after injection. They remained greatly elevated for several days in rabbit 42.

As has been stated, serial counts were not begun on the group of rabbits which received repeated injections of protagon until the daily dosage of the group had reached 0.5 gm. This procedure revealed differences in the intensity of the reactions among different members of the group, which were apparently dependent upon the number of

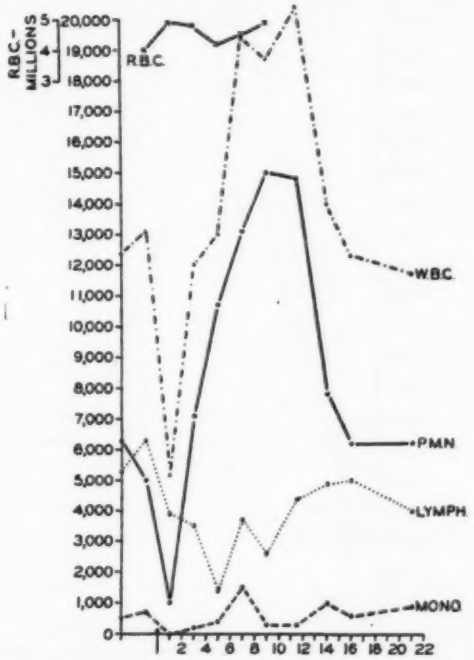


CHART 2. Rabbit 5. Counts of the red and white blood cells following injection of 0.5 gm. of protagon on the 52nd day after daily injections were started. The intensity of the reaction is estimated as ++++.

preceding injections. The reaction of the white blood cells following an injection proved to be more intense in those rabbits of the group which were counted earliest, although the reactions were the same qualitatively in all cases (cf. charts 1 and 2 with 4, A). Furthermore, the first counts on any given rabbit of the group were of greater intensity than the later ones on the same animal (cf. charts 3, A, B, C

and 4, A, B). Both of these observations pointed toward establishment of either tolerance, or inability to respond. In line with these findings is the fact that the reactions in rabbits 33 and 42 (chart 5), which were given first injections of 0.2 gm., or less, of protagon, were as intense as the late reactions to much larger doses on the part of the

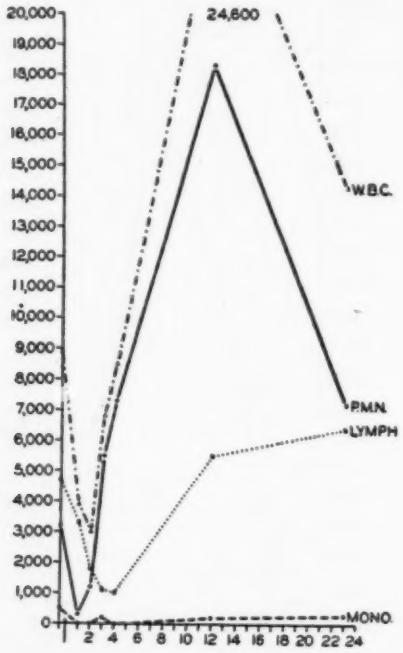


CHART 3, A. Rabbit 8. Counts of the white blood cells following injection of 0.5 gm. of protagon on the 47th day after daily injections were started. The intensity of the reaction is estimated as ++++.

rabbits which were given daily injections; and also the fact that a first injection of 0.5 gm. to rabbit 32 proved lethal within half an hour, despite the fact that that amount was tolerated over long periods of time by the rabbits to which the lipoids were given in gradually increasing amounts.

Qualitative changes in the blood cells also occurred characteristically

following the injections. "Non-motile" and even disintegrating granulocytes were frequently observed in the supravital smears for three

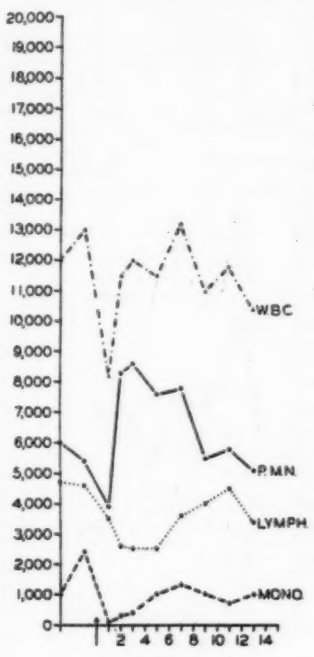


CHART 3B

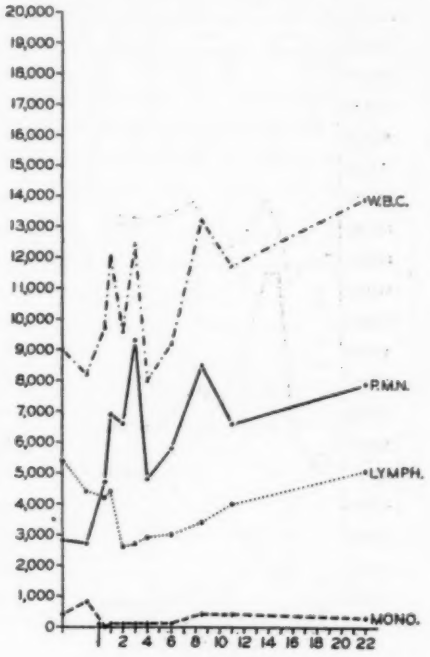


CHART 3C

CHART 3, B. Same rabbit as chart 3, A. Counts of the white blood cells after injection of 0.5 gm. of protagon on the 60th day after daily injections were started. The intensity of the reaction was considerably less than that on the 47th day of the injections (cf. chart 3, A). It is estimated as ++.

CHART 3, C. Same rabbit as charts 3, A and B. Counts of the white blood cells after injection of 0.6 gm. of protagon on the 64th day after the injections were started. Despite the greater dose of protagon, the intensity of the reaction is somewhat less than that on the 60th day of the injections, and considerably less than that on the 47th day. It is estimated as +.

or four hours after an injection; and new ones, with young granules and few lobes to the nucleus, from the third till the ninth hours. "Non-motile" cells are met only infrequently, normally; and disin-

tegrating ones, practically never. From the fifth hour, the polymorphonuclears and monocytes contained prominent phagocytic vacuoles,

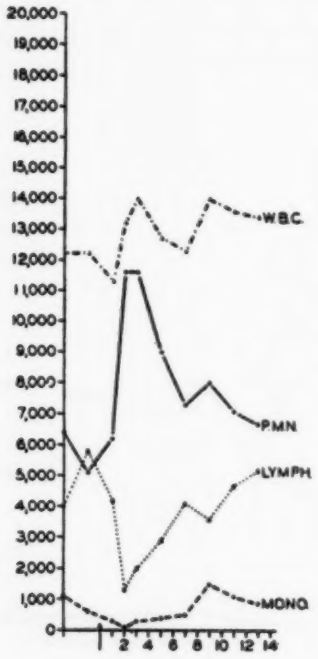


CHART 4A

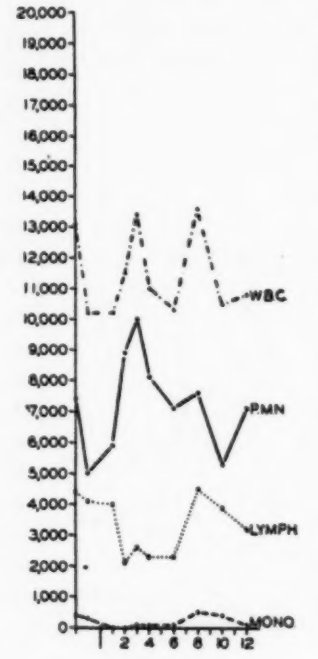


CHART 4B

CHART 4, A. Rabbit 13. Counts of the white blood cells after injection of 0.5 gm. of protagon on the 60th day after the injections were started. The reaction is less intense than the reactions of rabbits studied earlier in the course of the injections (cf. charts 4, 5 and 3, A). It is estimated as +++.

CHART 4, B. Same rabbit as chart 4, A. Counts of the white blood cells after injection of 0.7 gm. of protagon on the 68th day after the injections were started. Despite the greater dose of protagon, the intensity of the reaction is less than that on the 60th day of the injections. It is estimated as +.

which were larger and more acid in reaction than normal, and suggestive of the vacuoles characteristic of the macrophages in the tissues in these experiments (14). Fragments of red cells were met in ab-

TABLE I

*The Reactions of the White Blood Cells to Intravenous Injections of Protagon*[a]

(Absolute numbers in fractions of 1,000)

| NEAREST HOUR AFTER THE INJECTION | NUMBER OF RABBIT | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 | 10 | 9 | | 32* | 33 | 34† | 6 | 10 | 9 | | 32* | 33 | 34† | 6 | 10 | 9 | | 33 | 34† | 6 | 10 | 9 | | 33 | 34† |
| | Days since injections were begun | | | | | | | Grams injected | | | | | | | Estimated intensity of reaction | | | | | | W.B.C. | | | | | |
| | 49 | 52 | 63 | 68 | 0 | 0 | 0 | 0.5 | 0.5 | 0.5 | 0.7 | 0.5 | 0.1 | 0.2 | ++++ | ++++ | ++ | + | ++ | ++ | | | | | | |
| | W.B.C. | | | | | | | P.M.N. | | | | | | | Lymphocytes | | | | | | Monocytes | | | | | |
| Before | 16.2 | 13.0 | 7.8 | 11.8 | | 6.0 | 4.5 | 5.2 | 6.0 | 3.1 | 4.4 | | 2.6 | 2.6 | 7.0 | 5.3 | 3.8 | 6.5 | 1.6 | 0.7 | 1.7 | 0.5 | 0.7 | 0.2 | 0.7 | 0.4 |
| ½ | | | 7.2 | | | 4.0 | 3.1 | | | 3.0 | | | 2.5 | 1.6 | | | 2.5 | | 1.1 | 1.1 | | | 0.6 | | 0.0 | 0.0 |
| 1 | 4.9 | 6.4 | 7.6 | 8.0 | | | | 1.0 | 1.4 | 6.2 | 3.6 | | | | 3.5 | 3.8 | 1.3 | 4.3 | | | 0.1 | 0.1 | 0.0 | 0.0 | | |
| 1½ | | | | | | 8.9 | 4.8 | | | | | | 7.9 | 3.7 | | | | | 0.6 | 1.0 | | | | | 0.1 | 0.0 |
| 2 | 6.4 | | | 10.8 | | | | 2.2 | | | 5.9 | | | | 2.9 | | | 4.2 | | | 0.4 | | | 0.1 | | |
| 2½ | | | 12.2 | | | 8.7 | 8.3 | | | 10.3 | | | 7.5 | 7.3 | | | 1.8 | | 1.0 | 0.7 | | | 0.1 | | 0.0 | 0.0 |
| 3 | 6.6 | 10.0 | 10.7 | 11.4 | | | | 3.8 | 8.1 | 8.7 | 5.9 | | | | 2.5 | 1.4 | 1.5 | 4.8 | | | 0.3 | 0.1 | 0.1 | 0.3 | | |
| 4 | 8.9 | | | 13.1 | | 8.6 | 9.6 | 5.7 | | | 5.9 | | 7.9 | 8.6 | 2.7 | | | 4.5 | 0.3 | 0.6 | 0.1 | | | 1.1 | 0.0 | 0.0 |
| 5 | 11.1 | 13.9 | 11.4 | | | 7.5 | 9.7 | 8.1 | 10.8 | 8.2 | | | 5.8 | 8.8 | 2.2 | 1.7 | 2.7 | | 0.6 | 0.5 | 0.4 | 0.3 | 0.0 | | 0.2 | 0.0 |
| 6 | 14.2 | | 7.9 | 11.9 | | | 8.8 | | | 4.9 | 4.7 | | | 8.1 | | | 2.3 | 5.1 | | 0.4 | | | 0.2 | 1.3 | | 0.0 |
| 7 | 13.2 | 19.0 | | | | 6.7 | 11.7 | 8.6 | 13.2 | | | | 5.5 | 9.8 | 2.4 | 3.7 | | | 0.6 | 1.0 | 1.5 | 0.4 | | | 0.0 | 0.1 |
| 8 | | | 9.4 | 9.8 | | | | | | 6.7 | 4.6 | | | | | | 1.9 | 4.0 | | | | | 0.6 | 0.6 | | |
| 9 | 19.4 | 15.6 | | | | 5.9 | 10.1 | 14.8 | 8.9 | | | | 4.0 | 8.4 | 2.6 | 4.8 | | | 0.9 | 0.6 | 0.8 | 0.8 | | | 0.3 | 0.1 |
| 10 | | | 8.4 | 15.1 | | | | | | 6.0 | 5.1 | | | | | | 1.8 | 8.3 | | | | | 0.3 | 0.7 | | |
| 11 | | | | | | 8.6 | 8.9 | | | | | | 5.8 | 7.0 | | | | | 1.5 | 0.4 | | | | | 0.2 | 0.4 |
| 12 | 15.6 | 14.8 | 7.1 | 11.4 | | | | 10.2 | 7.3 | 4.3 | 2.7 | | | | 4.5 | 5.9 | 2.1 | 7.7 | | | 0.3 | 0.5 | 0.4 | 0.7 | | |
| 13 | | | | | | 7.9 | 9.1 | | | | | | 5.5 | 8.0 | | | | | 1.1 | 0.4 | | | | | 0.4 | 0.1 |
| 14 | | 16.0 | | | | | | | 8.1 | | | | | | | 5.9 | | | | | | 0.6 | | | | |
| 15 | | | | | | | 6.4 | | | | | | | 5.3 | | | | | | 0.4 | | | | | | 0.0 |
| 16 | | 11.0 | | | | | | | 5.7 | | | | | | | 3.2 | | | | | | 0.8 | | | | |
| 17 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 18 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 19 | | | | | | | 5.5 | | | | | | | 4.6 | | | | | | 0.4 | | | | | | 0.1 |
| 20 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 21 | 17.8 | 10.9 | | | | | | 11.5 | 4.3 | | | | | | 3.4 | 5.1 | | | | | 0.5 | 0.4 | | | | |
| 22 | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 23 | | | 8.7 | | | 7.9 | 6.1 | | | 3.9 | | | 4.0 | 5.1 | | | 4.0 | | | 0.4 | | | 0.4 | | 0.5 | 0.1 |
| 24 | | | | | | | | | | | | | | | | | | | | | | | | | | |

* Rabbit 32 had not received protagon previously. She died within 30 minutes of the injection (0.5 gm.)

† The protagon used for this rabbit was the same as that used for rabbit 42 (chart 5). It had been treated for the removal of water-soluble impurities.

[a] This table includes only those experiments which are not recorded by charts.

normal numbers in the first few hours after an injection in those instances in which the reaction of the white cells was striking. Nucleated red cells occurred occasionally in the pre-injection smears; they

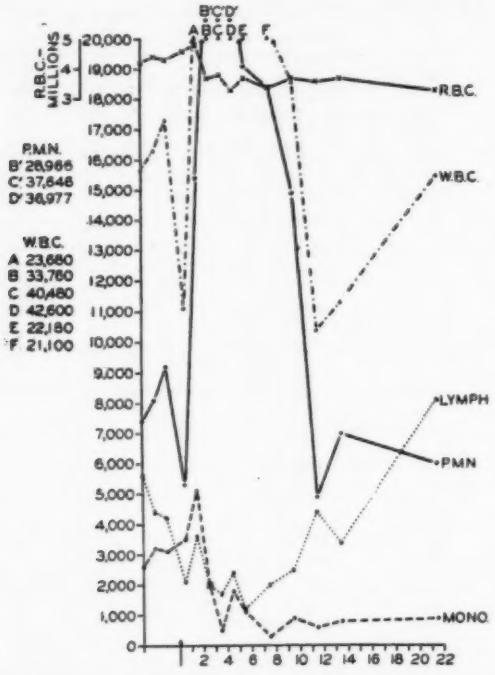


CHART 5. Rabbit 42. Counts of the red and white blood cells following injection of only 0.15 gm. of protagon which had been treated for removal of water soluble impurities. This rabbit had not received previous injections of protagon. The intensity of the reaction is greater than in any of the rabbits which had received daily injections of protagon (cf. charts 1 and 2). It is estimated as ++++.

usually occurred frequently during the first twelve hours following an injection.

Charts 2 and 5 and Table II present the data from the serial counts of the red blood cells following individual injections of protagon. The counts fluctuated somewhat during the first hour and a half

following the injections, with a tendency toward increase, but returned to normal thereafter. At times they decreased about five hours after

TABLE II

*Red Blood Counts following Intravenous Injections of Protagon*[3]

(Counts in fractions of 1,000)

| NEAREST HOUR AFTER THE INJECTION | NUMBER OF RABBIT | | |
|---|---|---|---|
| | 10 | 33 | 34 |
| | Days since injections were begun | | |
| | 52 | 0 | 0 |
| | Grams injected | | |
| | 0.5 | 0.1 | 0.2 |
| Before | 4,850 | 5,105 | 5,455 |
| ½ | | 4,862 | 4,845 |
| 1 | 5,280 | | |
| 1½ | | 5,018 | 5,635 |
| 2 | | | |
| 2½ | | 4,845 | 5,390 |
| 3 | 4,570 | | |
| 4 | | | 5,510 |
| 5 | 3,910 | 4,855 | |
| 6 | | | 5,430 |
| 7 | 4,080 | 5,090 | |
| 8 | | | |
| 9 | 4,050 | 4,970 | 5,415 |
| 10 | | | |
| 11 | | 4,850 | |
| 12 | | | |
| 13 | | | 6,100 |
| 14 | | | |
| 15 | | | 6,595 |
| 16 | | | |
| 17 | | | |
| 18 | | | |
| 19 | | | 6,460 |
| 20 | | | |
| 21 | 3,420 | | |
| 22 | | | |
| 23 | | | 6,445 |
| 24 | | | |

the injections, but this event was variable. The qualitative effects upon the red cells were described above. They were apparently independent of the effects upon the red blood counts.

Counts of the white blood cells over twenty-four hour periods following intravenous injections of sodium nucleinate, according to the technique described by Doan, Zerfas, Warren and Ames (3), were carried out on two control rabbits (nos. 15, 18) and, also, at the termination of the experiment on rabbit 2, which had received repeated

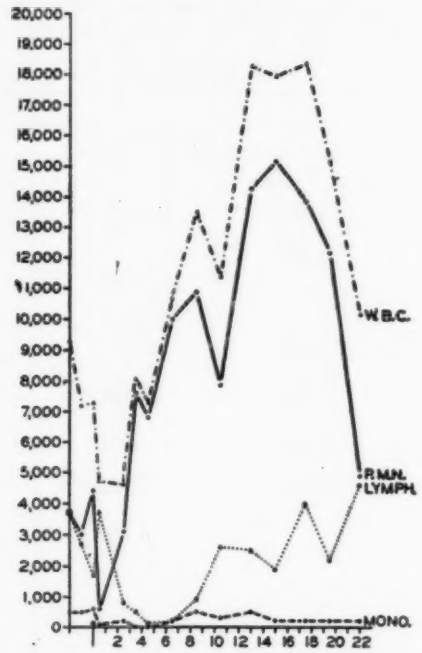


CHART 6. Rabbit 18. Counts of the white blood cells following injection of 1.0 gm. of sodium nucleinate. The effects upon the white blood cells, and the time at which they occurred in relation to the injections, are identical to the effects from protagon shown in charts 1, 2, 3 and 4. The intensity of the reaction is estimated as ++++.

injections of small amounts of the experimental lipoids for the preceding 63 days (14). Chart 6 and table III present these data. The reactions of the blood cells to the nucleinate proved to parallel the reactions to the experimental lipoids in every respect. This is true not only for the two control rabbits, but also for rabbit 2. The simi-

larity is especially obvious in the more intense reactions to protagon (cf. chart 6 with charts 1, 2 and 5). The same sequence of events in

TABLE III

*The Reaction of the White Blood Cells to Intravenous Injections of Sodium Nucleinate*[a]
(Absolute numbers in fractions of 1,000)

| NEAREST HOUR AFTER THE INJECTION | NUMBER OF RABBIT | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 | 15 | 2 | 15 | 2 | 15 | 2 | 15 |
| | | | Grams injected | | | | | |
| | | | 1.0 | 1.0 | | | | |
| | W.B.C. | | P.M.N. | | Lymphocytes | | Monocytes | |
| Before | 7.3 | 10.5 | 3.0 | 5.6 | 3.1 | 3.6 | 0.4 | 0.8 |
| ½ | 4.4 | | 0.8 | | 3.2 | | 0.1 | |
| 1 | | 5.4 | | 2.1 | | 2.9 | | 0.2 |
| 1½ | 1.8 | | 0.3 | | 1.5 | | 0.0 | |
| 2 | | 5.0 | | 2.3 | | 2.3 | | 0.1 |
| 2½ | 1.5 | | 0.7 | | 0.7 | | 0.1 | |
| 3 | | 5.6 | | 4.3 | | 1.0 | | 0.2 |
| 4 | 2.4 | 8.1 | 1.8 | 7.7 | 0.4 | 0.3 | 0.0 | 0.1 |
| 5 | 4.1 | 6.5 | 3.5 | 6.3 | 0.5 | 0.1 | 0.0 | 0.0 |
| 6 | 4.2 | 12.6 | 3.6 | 11.7 | 0.1 | 0.1 | 0.1 | 0.3 |
| 7 | 7.0 | | 5.9 | | 0.5 | | 0.1 | |
| 8 | 11.1 | 14.0 | 9.5 | 11.5 | 0.8 | 0.9 | 0.3 | 0.7 |
| 9 | 9.3 | | 7.7 | | 1.0 | | 0.1 | |
| 10 | 11.7 | 12.5 | 9.2 | 9.3 | 1.4 | 0.6 | 0.6 | 1.2 |
| 11 | 17.2 | | 14.5 | | 1.3 | | 0.6 | |
| 12 | 18.0 | 27.9 | 14.7 | 21.5 | 1.9 | 4.9 | 0.5 | 0.6 |
| 13 | 14.4 | | 11.8 | | 1.1 | | 0.8 | |
| 14 | 21.6 | 25.0 | 18.2 | 17.8 | 2.0 | 5.6 | 0.3 | 0.8 |
| 15 | | | | | | | | |
| 16 | | 26.0 | | 13.4 | | 11.2 | | 0.4 |
| 17 | | | | | | | | |
| 18 | | 24.5 | | 15.0 | | 8.2 | | 0.7 |
| 19 | | | | | | | | |
| 20 | 18.8 | 18.0 | 11.5 | 10.1 | 5.0 | 6.6 | 0.8 | 0.6 |
| 21 | | | | | | | | |
| 22 | | 12.8 | | 6.3 | | 5.7 | | 0.3 |
| 23 | | | | | | | | |
| 24 | | 16.6 | | 8.5 | | 6.2 | | 0.7 |

the counts of both neutrophiles and lymphocytes occurred at comparable intervals of time after injection of the nucleinate as after injection of protagon. Furthermore, the qualitative features were

also similar. The first few hours after an injection of the nucleinate were characterized by the occurrence of "non-motile" and disintegrating granulocytes in circulation, and also of fragments of erythrocytes. These events were succeeded by the appearance of young polymorphonuclears, and at times of nucleated red cells.

Control counts of the white cells were made on six normal rabbits (nos. 12, 15, 16, 17, 18 and 19) over twenty-four hour periods following intravenous injections of the menstrum used for emulsification, i.e., 5 per cent glucose. This was sterilized in the same manner as the experimental emulsions, and was given in amounts of 14–20 cc. Diurnal counts were also made on rabbits 15 and 17. For purposes of brevity these data are not recorded. Very little fluctuation was observed in the diurnal counts, and no indication of the definite diurnal shifts which Das Gupta (1) obtained. This is probably indicative of the constancy of the environment in these experiments, and of the emotional poise of the rabbits. The counts following the injections of glucose were also practically without fluctuations during the first twenty hours following the injections, although elevations occurred characteristically after that. It is obvious, therefore, that the counts following injection of the experimental lipoids were not influenced by the menstrum used for emulsification. Qualitative changes in the red and white cells were not observed in either the diurnal or glucose studies.

Serial counts of the white blood cells were made after intravenous injections of egg lecithin in order to compare the effects following injections of the experimental mixture of galactolipids and sphingomyelins with those obtained by injections of a phospholipid alone. For this purpose serial counts were made on rabbit 28 after a single injection of 0.5 gm. of egg lecithin, and following individual injections of three rabbits (nos. 24, 25 and 26), which were receiving daily intravenous injections of the same lot of lecithin in a different series of studies (13). The serial counts in the latter case were not begun until the daily doses of the group were 0.7 gm. or more. Charts 7 and 8, and table IV present these data. The effects of injections of lecithin on the blood cells were transient and totally different from those obtained by injections of protagon. Slight leucocytoses, accompanied by increase of both granulocytes and lymphocytes, occurred within

the first half hour after an injection. These were soon followed by return to the pre-injection levels without further change, and are considered to have been due entirely to redistribution secondary to injection.

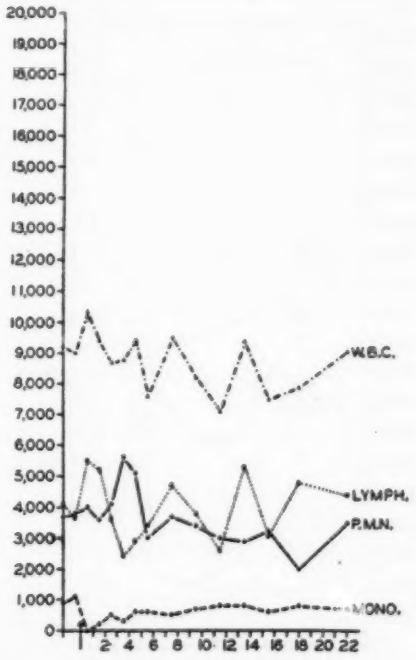


CHART 7. Rabbit 26. Counts of the white blood cells following injection of 1.0 gm. of egg lecithin on the 21st day after daily injections were begun. The effect upon the blood cells, both immediately and in the succeeding 24 hours after the injection, is totally different from the effects of protagon at comparable periods of time (cf. charts 1, 2 and 5).

The experimental data therefore indicate that intravenous injections of the biologic mixture of cerebrosides and sphingomyelins that occurs in the ether insoluble fraction of brain lipoids produce the same effects upon the white blood cells as are produced by injections of sodium nucleinate, and that the intensity of the reaction eventually

decreases with prolonged repetition. The red cells, on the other hand, suffer little effect from the injections. Diurnal counts, counts following injections of glucose alone, and counts following injections of lecithin yielded entirely different curves from those obtained by the experimental injections.

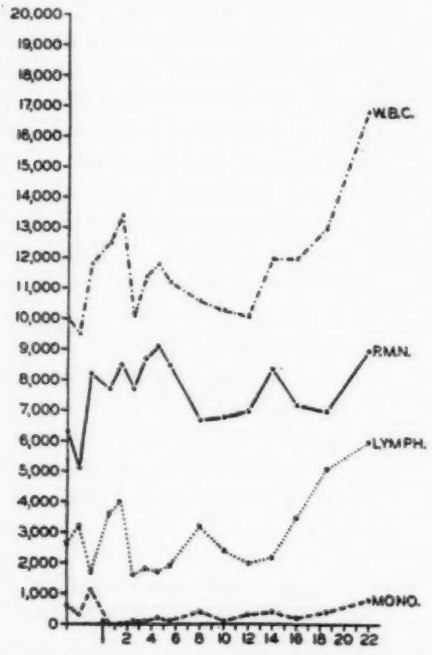


CHART 8. Rabbit 28. Counts of the white blood cells after injection of 0.5 gm. of egg lecithin. This rabbit had not received previous injections. In contrast to the effects from injections of protagon to rabbits which had not been previously injected, injection of lecithin in this rabbit had no greater effect, either immediately or in the succeeding 18 hours, than that shown by rabbits habituated to lecithin (cf. chart 7).

The tissue studies and periodic blood counts of the rabbits of this series which received daily injections of protagon have been reported (14). Only those findings which seem pertinent to the present studies will be reviewed. Sustained leucocytosis developed gradually, and

was accompanied by increase of both neutrophiles and lymphocytes (cf. charts I and II of reference 14 on rabbits 4 and 13, respectively).

TABLE IV

*The Reaction of the White Blood Cells to Intravenous Injections of Egg Lecithin*[3]

(Absolute numbers in fractions of 1,000)

| NEAREST HOUR AFTER THE INJECTION | NUMBER OF RABBIT | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 24 | 25 | 24 | 25 | 24 | 25 | 24 | 25 |
| | Days since injections were begun | | Grams Injected | | | | | |
| | 42 | 41 | 1.0 | 0.8 | | | | |
| | W.B.C. | | P.M.N. | | Lymphocytes | | Monocytes | |
| Before | 9.7 | 10.6 | 3.6 | 3.4 | 4.2 | 3.1 | 0.9 | 1.6 |
| ½ | 10.7 | 10.9 | 5.4 | 5.9 | 4.3 | 3.5 | 0.0 | 0.0 |
| 1 | | | | | | | | |
| 1½ | 8.6 | 12.5 | 4.3 | 6.5 | 2.9 | 3.9 | 0.3 | 0.6 |
| 2 | | | | | | | | |
| 2½ | 9.7 | | 5.1 | | 3.1 | | 0.7 | |
| 3 | | 8.9 | | 4.2 | | 1.8 | | 1.4 |
| 4 | 8.5 | 11.9 | 5.2 | 5.0 | 2.0 | 4.1 | 0.6 | 1.0 |
| 5 | 9.7 | 9.2 | 4.3 | 2.2 | 3.1 | 3.5 | 1.0 | 1.0 |
| 6 | 8.9 | 10.4 | 4.9 | 4.6 | 2.6 | 3.3 | 0.4 | 0.8 |
| 7 | | | | | | | | |
| 8 | 9.0 | 7.8 | 4.1 | 2.0 | 3.0 | 2.5 | 0.9 | 1.3 |
| 9 | | | | | | | | |
| 10 | 8.6 | 7.4 | 4.0 | 2.7 | 2.9 | 2.4 | 0.7 | 1.0 |
| 11 | | | | | | | | |
| 12 | 9.0 | 7.2 | 3.8 | 2.1 | 3.2 | 2.6 | 0.9 | 1.0 |
| 13 | | | | | | | | |
| 14 | 8.6 | 6.9 | 4.3 | 2.1 | 2.7 | 1.9 | 0.8 | 1.5 |
| 15 | | | | | | | | |
| 16 | 8.5 | 6.3 | 4.5 | 1.4 | 2.5 | 3.2 | 1.0 | 0.7 |
| 17 | | | | | | | | |
| 18 | 8.6 | | 4.4 | | 3.1 | | 0.7 | |
| 19 | | 6.6 | | 1.6 | | 3.1 | | 0.7 |
| 20 | | | | | | | | |
| 21 | | | | | | | | |
| 22 | 8.9 | 7.0 | 3.6 | 2.0 | 3.6 | 3.0 | 1.1 | 0.8 |
| 23 | | | | | | | | |
| 24 | | | | | | | | |

The bone marrow was hyperplastic with increased activity of the granulocytic centers at late levels of maturation, with increased

myeloid-erythroid ratios, with hyperplasia of the reticular cells and with shrinkage of fat cells. Extramedullary hematopoiesis was not observed. Hyperplasia of reticular cells and infiltrations of characteristic macrophages were generalized. These were most extensive in the spleen and were accompanied by depletion of the Malpighian corpuscles and compression of the sinusoids. The lungs were diffusely and extensively infiltrated with foam cells with marked thickening of the alveolar septa and reduction of alveolar space.

## DISCUSSION

Doan, Zerfas, Warren and Ames (3) found that the reaction of the white blood cells to an intravenous injection of sodium nucleinate is characterized by a short period of leucopenia followed by a prolonged period of leucocytosis. They concluded that the leucopenia is due to stasis of neutrophiles within the spleen, without abnormal destruction, while the leucocytosis is due to specific chemotaxis of the drug for granulocytes. Conversion of the nucleinate into the simpler adenine and guanine nucleotides, resulted in loss of the leucopenic factor but retention of the chemotactic one in both compounds. They sometimes observed a decrease in lymphocytes, as well as of granulocytes, during the leucopenic phase, but failed to obtain it invariably. Doan continued his studies with these substances and found that daily injections of neucleotides (4) or nucleinate (5) give rise to sustained neutrocytosis and myeloid hyperplasia of the bone marrow. He came to the conclusion that: "(1) nucleic acid and its degradation products exert an immediate chemotactic effect on normal myeloid foci with a prompt, effective increase in the delivery of mature neutrophils to the circulation under a controlled rhythmic mechanism; (2) a short course of injections of the pentose nucleotides has resulted in the multiplication and maturation of myelocytes in normal marrow, without injury to the integrity of this or other organs of the body, and this reaction has been responsible for the neutrophilic leucocytosis observed in the blood stream; (3) repeated large intravenous injections of the nucleinate molecule have neither tended to exhaust the myelopoietic potentialities of marrow nor to cause a malignant hyperplasia of these elements in normal rabbits." In addition to the effect on the granulocytes, he obtained unexplained

lymphopenias with the nucleinate. He did not investigate the intensity of reactions to individual injections as the series progressed.

Reznikoff (10) extended these studies to both complex and simplified purine compounds from other sources. He obtained the characteristic leucocytosis in each instance but found it to be invariably preceded, however, by a period of leucopenia. He (11) recommended the use of nucleic acid derivatives in selected cases of agranulocytosis. Jackson, Parker, Rinehart and Taylor (7) supported the same recommendation a year later, and Doan (4) two years later.

Widespread use of pentnucleotides followed these reports. Failure on the part of numerous workers to obtain the desired results led Das Gupta (1) to investigate the matter further by comparing the curves of the white blood cells of rabbits after injections of nucleic acid derivatives with those obtained from injections of histamine, acetylcholine, adrenaline and a variety of other agents "reputed to be leucopoietic," but which, in actuality, exert definite effects upon the blood vascular system. He came to the conclusion that the effects of the nucleic acid derivatives upon the white blood cells are not the result of a specific stimulus to the myeloid centers, but are characteristic of a variety of agents capable of shifting the distribution of cells, and of calling forth preformed neutrophils from the marrow. He based his belief that they are not specifically leucotactic upon his failure to obtain sustained leucocytoses from a short series of repeated injections.

In the meantime Drury (6) and his collaborators demonstrated the pharmacologic activity of adenine, and its right to be classified with acetylcholine and histamine as one of the depressant substances present in tissues. This finding lends support to the contention of Das Gupta, but it must be recalled that guanine nucleotide, on the other hand, has questionable depressant activity and yet affects the white blood cells in the same way as does adenine nucleotide.

The present studies after injections of the ether insoluble fraction of brain lipoids reveal effects upon the white blood cells and bone marrow which are identical to those obtained by injection of sodium nucleinate. That these effects are not due to inclusion of nucleic acid derivatives or to histamine is evident from the absence of pentose, and the negative test for the imidazol group, respectively. That they

may be due to inclusion of other water soluble products from tissues seems unlikely, both because of the manner of preparing the stock solution (filtration after solution in fat solvents), and because the specific activity was retained after a portion of the stock solution had been treated for removal of water soluble impurities. The technique employed for this latter procedure included precipitation of the lipoids with acetone, and inclusion of a substance which is acetone insoluble, even though water soluble, is, of course, possible. The depressant substance which Weber, Nanninga and Major (16) isolated from brains, is therefore to be considered, but can not be intelligently discussed until more is known of its identity, or of the factor in protagon which elicits the reactions of the white blood cells obtained in the present studies.

Acute anaphylaxis has been found to affect the blood cells (2) in the same way as in these experiments, and to be associated with stasis of neutrophils in the lungs (15). Anaphylaxis seems out of the question in these experiments on several scores: animals tolerated less of the material on first injection than later; the sequence of the injections was such as to prevent the development of allergy; other manifestations of allergy were not observed.

Since injections of lecithin failed to elicit similar effects upon the white blood cells, the effects from injections of protagon can not be regarded as due to lipoids, *per se*, to colloids, to phosphatides, or to the phosphoric-choline linkage. It seems possible, therefore, that the effects are due, specifically, to either the cerebroside component of the experimental mixture, or the sphingosin-lignoceric radicle common to both components of the mixture. The fact that subcutaneous injection of the galactolipids resulted in excessive local infiltrations of polymorphonuclear cells, in contrast to stimulation of mononuclear cells by similar injections of sphingomyelin (12), makes the former possibility seem the more likely.

In their investigation of the effects of nucleic acid derivatives upon the white blood cells, Doan, Zerfas, Warren and Ames (3) found that decrease of lymphocytes occurred inconstantly during the period of leucopenia, but that this was never followed by an increase of lymphocytes. He therefore yielded the lymphocytes little consideration. In the experiments with nucleinate in the present report, and in one

experiment with the same substance which Das Gupta reported, decrease in lymphocytes and compensatory increase were definite, and followed the exact pattern of the same events after injection of the brain lipoids. Reznikoff (10) obtained a decrease in lymphocytes after injection of the purine derivatives which he employed, but he used phosphates as a buffer, and since solutions of them alone cause decrease in lymphocytes, he apparently assumed that the decrease in his experiments was secondary to the buffer. The explanation for the greater prominence of the reactions of the lymphocytes in these cases than in Doan's experience is not evident. From analysis of the data, however, it seems as if the effect upon the lymphocytes is probably of equal significance to the effect upon the granulocytes. That similar decrease in lymphocytes occurs in anaphylactic shock adds weight to this concept. In each case the decrease in lymphocytes begins slightly later than the decrease in granulocytes and far outlasts it. In each case the decrease progresses as the neutrocytosis develops, and usually continues until shortly before its peak. At that time the lymphocytes begin to increase gradually, with return to normal during the hours that the neutrocytosis is slowly receding. The return of the lymphocytes to normal is usually followed by definite compensatory lymphocytosis, suggestive of preceding stimulation to production. Curves of the two types of cells during reactions to either nucleinate or the brain lipoids present almost mirrored images of each other (charts 1, 2, 5 and 6). The explanation of this entire reaction—neutropenia, lymphopenia, neutrocytosis, lymphocytosis, time relationships to injection and to each other—is not evident, but it is so consistent, and so definite, that it would seem to be the expression of some fundamental biologic activity resulting in removal of cells from circulation and replacement of new ones in excessive quantities, the time for replacement varying with the cell replaced.

While the mixture of brain lipoids used in the present studies had the same effects upon blood and marrow as does sodium nucleinate, it exhibited characteristics that have not been investigated for the nucleic acid derivatives. The effects from single injections of the mixture lost their intensity with daily repetition, although there was no evidence of lessened stimulus to sustained leucocytosis and myeloid hyperplasia. It would therefore seem that increased tolerance, or

inability to react, to the immediate effects of the material was in some way established, but not to the more latent and prolonged effects. This concept was further borne out by the fact that doses easily tolerated by animals accustomed to the material were lethal to new animals.' The reactions of the tissues in these experiments varied from those reported by Doan after repeated injections of nucleic acid derivatives in several important respects. In particular, the spleens and lungs were diffusely and extensively infiltrated with macrophages with great reduction of sinusoidal space in the first instance, and packing of the septa and reduction of the alveolar space in the second. Furthermore, the reticulo-endothelial cells had stored great quantities of the experimental material. It is possible that the lessened intensity of the immediate reactions to individual injections, with continued stimulus to sustained leucocytosis and myeloid hyperplasia, lies in the progression of these events. It seems possible that the immediate reaction to a single injection of these substances, and the prolonged effects may differ somewhat in nature, that the former may be the characteristic expression of a basic biologic activity, as discussed above, while sustained leucocytosis and myeloid hyperplasia may be secondary to the frequency of repetition or the prolongation of the stimulus. In the case of the brain lipoids it seems probable that they may have eventually functioned almost chronically by virtue of storage throughout the reticulo-endothelial system.

## SUMMARY

1. Intravenous injections of rabbits with the ether insoluble fraction of brain lipoids (protagon) produced the same effect upon the white blood cells and bone marrow as are produced by intravenous injections of sodium nucleinate.

2. Individual injections were followed by neutropenia within half an hour. This was succeeded by neutrocytosis which began within 1–4 hours of the injection, reached a peak within 2–12 hours of the injection and returned to normal within 8–24 or more hours of the injection. Decrease of lymphocytes began slightly later than that of the neutrophils, but continued for 11–12 hours from the time of the injection. Thereafter the lymphocytes returned gradually to pre-injection levels, or higher, within 24 hours of the injection. The

monocytes tended to parallel the lymphocytes. These events in the counts were accompanied by fragmentation of neutrophils and erythrocytes until the 4th hour after the injection, and by the appearance of young neutrophils and increased numbers of nucleated red cells from the 3rd to the 8th hour after the injection. The red blood counts increased transitorily immediately after the injections, but exhibited no consistent changes thereafter.

3. Control counts after injections of glucose or of egg lecithin, and diurnal counts were totally different in character.

4. Repeated injections of the brain lipoids resulted in sustained leucocytoses accompanied by increase of both polymorphonuclears and lymphocytes, and by myeloid hyperplasia of the marrow.

5. Rabbits which had not received previous injections of the brain lipoids reacted more intensely to small doses, and did not tolerate as large doses as did rabbits given daily injections. In rabbits which received daily injections, the intensity of the reaction to individual injections of the series decreased as the duration of the injections increased. This lessened intensity to individual injections of the series was unaccompanied by indications of change in the myeloid activity or sustained leucocytoses.

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## BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

*Renal Lithiasis.* By CHARLES C. HIGGINS. 140 pp. Illus. $3.00. Charles C. Thomas, Springfield, Illinois, 1943.

This booklet is an amplified transcription of the Beaumont lectures of 1942 delivered by Dr. Higgins. A brief resume is given of the older observations on renal lithiasis. Especial emphasis is placed on the geographical distribution of urinary calculi and the vitamin deficiencies which are common in the regions of highest incidence. The author reviews his experimental observations on the production of urinary lithiasis in animals and, from these and clinical observations, offers his regimens for the handling of various types of kidney stones. A plea is made for careful chemical analysis of the calculi which are recovered.

J. E. H.

*Orthopedic Subjects.* Prepared and Edited by the Subcommittee on Orthopedic Surgery of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. GEORGE E. BENNETT, Chairman (and others). 306 pp. Illus. W. B. Saunders Company, Philadelphia and London, 1942. (Military Surgical Manuals, Vol. 4.)

This small, compact book was prepared for medical officers of the Armed Forces who might be faced with the task of administering orthopedic care with a minimal training, and to whom the aid of a specialist was not available. Circumstances have placed many civilian physicians in a similar position. The text is really a compilation of short monographs prepared by some of the leading authorities on orthopedic subjects, and the information is a concensus of the accepted principles of orthopedic surgery.

Not all aspects of orthopedic surgery are encompassed, and the discussion is limited to fractures and osteomyelitis. The material has been arranged as simply as possible, and numerous illustrations are included. Particular attention has been given to the basic principles so essential in obtaining satisfactory results in the surgery of bones, such as the physiology of bone healing and the mechanics of operations, including a section on the preparation and draping of the region for operation. Stress is laid upon the necessity for adequate preoperative and postoperative care to include the treatment of the patient as a whole as well as of the individual bones.

The book is devoted primarily to therapy, and all material has been condensed. The index is adequate for easy reference. Sections of the book are devoted to ununited fractures, injuries of the spinal column, compound fractures, and osteomyelitis; and each part includes divisions on emergency as well as definitive care.

The discussion of osteomyelitis includes the causes, pathological changes, and complications as well as the therapy of acute and chronic cases.

The civilian physician who finds it necessary to treat injuries and infections of the skeleton without the aid of the orthopedic surgeon, and the medical student who is being prepared to do so, will find this book an invaluable and authoritative aid.

J. L. III

*Textbook of Clinical Neurology.* By ISRAEL S. WECHSLER. 5th ed. 840 pp. Illus. $7.50. W. B. Saunders Company, Philadelphia and London, 1943.

This well known text book is now in its fifth edition. Much new material has been introduced including discussions of chemotherapy in meningitis, electroencephalography and recent work on the autonomic system. The point of view is purely clinical and the arrangement is that of Oppenheim. Little space is devoted to theoretical considerations and the presentations are straightforward and practical.

F. R. F.

*Anatomy of the Nervous System.* By STEPHEN WALTER RANSON. 7th ed. 520 pp. Illus. $6.50. W. B. Saunders Company, Philadelphia and London, 1943.

The seventh edition of this well known book was completed before the death of Dr. Ranson. The first edition appeared in 1920 and established itself immediately as a standard text book for students. Every effort has been made to keep it up to date. It is pleasant to know that Dr. Sam L. Clark of Vanderbilt University has been designated to take charge of further revisions.

The author has made extensive changes in the sections on the cerebellum, thalamus, hypothalamus, cerebral cortex and sympathetic nervous system. Recent studies of the thalamus and hypothalamus have clarified the anatomical connections and the new presentation is more satisfactory. The chapter dealing with the sympathetic system has been handled less well. It still emphasizes the antagonistic function of sympathetic and parasympathetic innervation which is an indefensible theory. There are several excellent new illustrations.

The chief value of this book has been simplicity and emphasis on relevent material. This point of view could be carried further with even more satisfactory results. If the term autonomic were substituted for sympathetic nervous system, the names sympathetic and parasympathetic would clearly designate the subdivisions. The separation of the fibers of the cranial nerves into seven components is based on comparative neurological theories that have no useful purpose for medical students. The motor nuclei could better be divided into two groups, somatic motor and autonomic; the sensory into two groups of special and general sensation. The designation of general visceral afferent and special visceral afferent nerve fibers is confusing and has no helpful anatomical or physiological basis.

O. R. L.

*Human Pathology.* By HOWARD T. KARSNER. 6th ed. 817 pp. Illus. $10.00. J. B. Lippincott Company, Philadelphia, 1942.

The subject matter in this new edition is vastly more comprehensive than in previous editions. A short section on the pathology of vitamin deficiencies has been added, as well as descriptions of diseases due to protozoa, spirochetal organisms, rickettsiae and filterable viruses. However, the virus diseases are not yet complete as yellow fever and various exanthemata are still missing. The effects of immunity and allergy in some diseases are included, but there is no general discussion of these subjects. The chapter on tumors has been rewritten and is particularly concise, yet comprehensive.

The material is again divided into general and systemic pathology. In the opinion of this reviewer this detracts from a clear-cut picture of any specific disease and at the same time results in unnecessary repetition.

The illustrations are abundant and good. The bibliography is complete and includes current publications. In general the medical student will find concentrated information on most pathological subjects readily available in this modern text-book.

E. H. O.

*Synopsis of Pathology.* By W. A. D. ANDERSON. 661 pp. Illus. $6.00. The C. V. Mosby Co., St. Louis, 1942.

In the preface the author recognizes the difficulties involved in writing a synopsis of pathology. He has succeeded admirably, however, in the opinion of this reviewer. The book is well written and very well illustrated. In the main, the author's intention to compose a concise synopsis of the essentials, unobscured by controversial details, has been nicely accomplished.

S. S. B.

*Family Treasures. A Study of the Inheritance of Normal Characteristics in Man.* By DAVID D. WHITNEY. 299 pp. Illus. $3.50. Jacques Cattell Press, Lancaster, Pa. 1942.

There are probably at least ten thousand people working on the improvement of man's environment and a billion dollars spent for the same purpose to every single investigator of man's heredity and to every scarce dollar intended for the eventual betterment or control of man's hereditary conditions by means of a greater knowledge thereof. The bulk of our hard-won information concerning human inheritance appertains to abnormal conditions, while of the exact mode of transmission of man's normal traits pitifully little has become known so far. The promising and most urgently needed *science* of eugenics has drifted into ill repute for many unfortunate reasons. Its enthusiastic promoters often snatched tentative findings from the few capable researchers long before conclusions were ripe for application to human propagation. In recent years and to an absurd degree Nazi doctrines abused and distorted eugenic aims and the modest first results of this legitimate young science. The army of social uplifters and Christianity in general concentrate their hopes for a new deal in euthenics and refuse to heed the lesson from the eugenic successes every farmer can obtain with his

live-stock even under poor environmental conditions. Last not least, much has been written concerning human heredity that should have remained in academic files to be tested and retested before being offered to the layman in popularized verbiage.

It was a great joy to hear of a new volume claiming to be "a study of the inheritance of normal characteristics in man." This joy was only slightly damped by the preface which states that this book is written for amateurs and is "a simple presentation." A glance at the index reveals that *normal* characteristics form only a part of the discussions and that another large share of the contents deals with the better known abnormalities, ranging from brachydactyly to stuttering. The initial joy dwindled still more at the discovery in the subject index of the puzzling item "Phi Beta Kappa," which was found to refer to a pedigree supposedly proving the inheritance of "superior intelligence" in a family in which the father and five of his children belonged to this scholastic society. Of the more than 200 large photographs the first encountered shows the "legs of average size of the parents transmitted to their daughter." The first random sample of text reads: "Are physicians, like poets, 'born and not made?' In some families all of the brothers may study medicine (Fig. 198), whereas in other families (Fig. 9, No. 10) only one may become a doctor of medicine." This question and its not very profound answer is followed by a discussion of heredity among "lovers of nature," accompanied by a plate of portraits of father and son who are "much interested in plants, animals and natural history." In a section devoted to the heredity of "Natural Charm and Grace of Manners" it is stated that "Girls attend 'charm classes' to get help in their personal relations with their associates. They receive the benefit of great efforts which are being made by a large group of people to aid them in their dress, in the arrangement of their hair," etc. A few lines below, the zoologist-author disillusions the amateur reader by reminding him that "charming manners are more than a veneer because they are, partially, at least, inborn traits (Fig. 200)." This admonition has for its sole scientific support figure 200 which shows a bearded father without necktie and his shaven son, both with their eyes deleted by a heavy line. The justification for this halftone picture (and for a great many others) is obscure, as it produces no evidence for the claims in the text nor does it seem to serve any educational or moral purpose. There is also the picture of a beautiful young lady and of her stately great-great-grandmother with the inscription "Styles of clothing . . . are acquired but leave no permanent impression on succeeding generations. . . ."

In one of the later chapters, dealing with Sex, it is stated that "Two parents insure variations, and since 'variety is the spice of life' there is no monotony in any family, community, country, or, indeed, in any part of the earth where there is man." By this time the reviewer began to feel that he had overestimated the intellectual ambitions of amateurs. According to Webster, however, *amateurish* can be defined as "superficial or defective like the work of an amateur." Since this is a book for amateurs and probably satisfies their needs, it need merely be mentioned that there is no place for this volume in a scientific library.

A. H. S.

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